PATTERN OF DRUG USE AND THEIR SAFETY PROFILE IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN A TERTIARY CARE HOSPITAL

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the requirements for the award of the degree of

M.D. PHARMACOLOGY

Branch VI

May 2019

CERTIFICATE

This is to certify that this dissertation entitled "**Pattern of drug use and their safety profile in the management of Chronic Obstructive Pulmonary Disease in a tertiary care hospital"** is a bonafide record of the work done by **Dr. Ramakrishnan. S.,** under my guidance and supervision in the Department of Pharmacology during the period of his postgraduate study for **M.D. Pharmacology [Branch-VI]** from 2016-2019.

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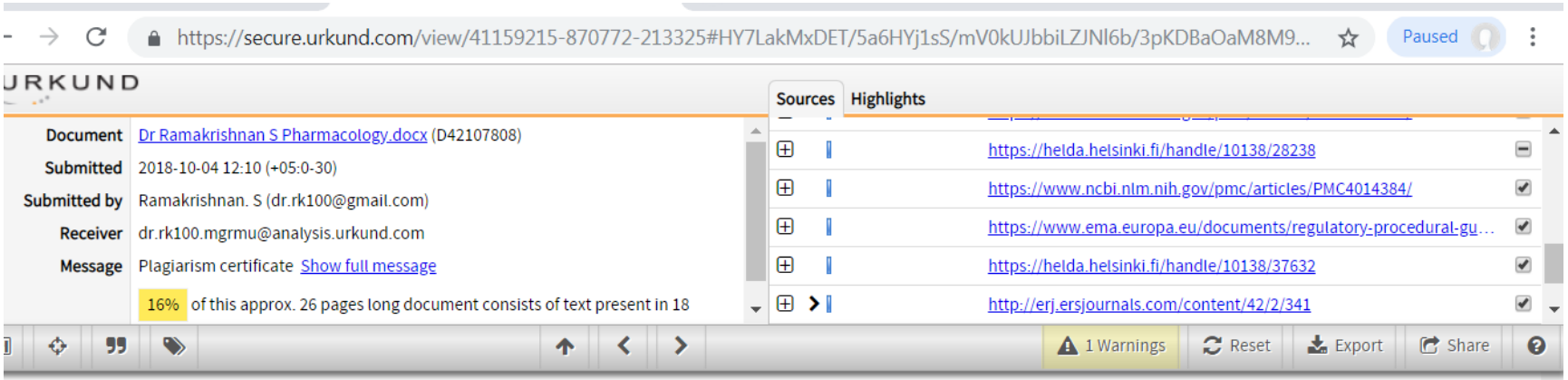

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CERTIFICATE – II

This is to certify that this dissertation work titled "**Pattern of Drug Use and their Safety Profile in the Management of Chronic Obstructive Pulmonary Disease in a Tertiary Care Hospital**" of the candidate **Dr. Ramakrishnan. S.,** with registration Number **201616352** for the award of **Doctor of Medicine** in the branch of **Pharmacology**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **16** percentage of plagiarism in the dissertation.

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Abbreviations

AATD	Alpha 1 antitrypsin deficiency
ADEs	Adverse drug events
ADR	Adverse drug reaction
AE	Adverse event
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AMP	Adenosine mono phosphate
BMI	Body mass Index
CB	Chronic bronchitis
CCHS	Copenhagen City Heart Study
COPD	Chronic obstructive pulmonary disease
DALYs	Disability adjusted life years
DH	Dutch hypothesis
DPI	Dry powder inhaler
DUS	Drug utilization study
EDL	Essential drug list
EOD	Environmental and occupational dusts
FDC	Fixed drug combination
FEV_1	Forced expiratory volume in 1 second
FGF	Familial and genetic factors
FVC	Forced vital capacity
GOLD	Global initiative for Chronic obstructive lung disease

HIC	High income countries
HRCT	High resolution computed tomography
ICS	Inhaled corticosteroids
IHEC	Institutional Human Ethics Committee
IRC	Institutional Research Committee
IV	Intravenous
LABAs	Long acting beta-2 agonists
LAMAs	Long acting muscarinic antagonists
LMICS	Low and middle income countries
LTOT	Long term oxygen therapy
LVRS	Lung volume reduction surgery
MDI	Metered dose inhaler
NPPV	Noninvasive positive pressure ventilation
OPD	Outpatient Department
PDE4	Phosphodiesterase 4
Pi	Protease inhibitor
PiM	Protease inhibitor M
PiMM	Protease inhibitor MM
pMDI	pressurized Metered Dose Inhaler
PPSV	Pneumococcal polysaccharide vaccine
PV	Pharmacovigilance
RT	Respiratory tract

SABA	Short acting beta-2 agonist
SAMA	Short acting muscarinic antagonist
SBLVR	Surgery and bronchoscopic lung volume reduction
SES	Socioeconomic status
SMI	Soft-mist inhaler
TSEP	Tobacco smoke and environmental pollution
WHO	World Health Organization
α1-AT	α1 Antitrypsin
α1-ATD	α1 Antitrypsin deficiency

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), the fourth leading cause of death worldwide, is a common evitable, manageable and progressive disease characterized by irreversible airflow restriction.[1] Pharmacotherapy in COPD usually involves usage of numerous drugs, thereby increasing the risk of adverse drug events (ADEs) proportionally. In COPD, pharmacotherapy is given to reduce symptoms, reduce frequency and severity of exacerbations, improve health status and exercise tolerance. Bronchodilators are the mainstay in the pharmacological management of COPD. Short acting bronchodilators are given for immediate relief from symptoms, one or more long acting bronchodilators (long acting beta 2 agonist [LAβAs]) or long acting muscarinic antagonist [LAMAs] are used for long term maintenance treatment in subjects with moderate to severe disease.

Inhaled corticosteroids (ICS) are the central of treatment of Asthma but in the management of COPD their role is controversial.[2-4] In COPD, the role of ICS is primarily to decrease the risk of exacerbations. The new GOLD strategy recommends the addition of second bronchodilator in patients with moderate airflow obstruction, reserving the ICS use in addition with a LABA and /or LAMA for patients with severe or very severe airflow obstruction and /or two or more exacerbations of COPD per year.[5,6] But there is evidence that prescriptions are not always written according to GOLD recommendations or other national guidelines, resulting in a high proportion of patients being

treated with ICS unnecessarily and exposed to the risk of side effects in undue manner.[7]

Adverse Drug Reaction (ADR) is defined by WHO, "As a response which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function". Most of the drugs produce some adverse effects and carry the potential for causing injury, even if used properly. As widely used drugs act by interfering with one or more aspects of molecular and cellular function, all of them have the risk of producing some reaction which may not be desirable all the times. Hence the goal of pharmacotherapy cannot be to prescribe a risk free regimen but to ensure that the risks of drug therapy are kept as low as possible. Proper data about the adverse effects of drugs help physicians to prescribe drugs, balancing the benefits and hazards.[8,9]

Inappropriate drug usage may preclude ideal benefit due to increased medical cost, antimicrobial resistance, adverse effects and mortality. Therefore drug utilization studies have become a plausible means in evaluating the healthcare systems. COPD management usually involves more than one drug which may escalate the risk of ADEs. The present study was aimed at assessing the current drug practice and ADEs in COPD management in General Medicine OPD.[10] Based on the total score, the drug-ADE association is termed definite, probable, possible or doubtful. Irrational use of drug and inappropriate prescription is the two common phenomena in the developing

countries which cause a big problem for providing effective health care facilities.

Many studies have been conducted in the past on respiratory diseases, however to our knowledge published data particularly focused on COPD especially in India is limited. It was indeed necessary to assess the approach of Indian pulmonologists in treating COPD patients in order to refine the treatment practice. Drug utilization audits ensure safe and correct usage of drugs, which can either be quantitative or qualitative or a combination of both. More efforts should be made to improve the prescribing of medication indicated for COPD so that they align with current guidelines. Bronchodilators are the mainstay of current management and the search to improve existing bronchodilators will continue; so also will the search for novel anti-inflammatory agents and therapeutic strategies to reverse the corticosteroid resistance seen in COPD. The present study aimed at assessing the current drug practice and ADEs in COPD management.[11-14]

Till date no study on pattern of drug use and their safety profile in the management of COPD has been conducted in this institution. Hence it was thought worthwhile to conduct a study to evaluate the pattern of drug use and their safety profile in the management of COPD in the General Medicine OPD of this institute.

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic obstructive lung disease (GOLD) as "a common preventable and treatable disease characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases."[15,16] The chronic airflow limitation typical of COPD is produced by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Emphysema or the destruction of lung alveoli is a pathological term which is frequently used clinically and narrates only one of many structural abnormalities seen in patients with COPD.

Chronic bronchitis is defined as the presence of chronic cough and sputum production for at least 3 months of the year for at least 2 consecutive years in the absence of any other disease.[16] Emphysema is defined as ''a condition of the lung characterized by permanent, abnormal enlargement of the respiratory airspaces, accompanied by destruction of their walls without obvious gross fibrosis.[17,18]

Theories related to aetiology of COPD

There are two hypotheses concerning the aetiology of COPD, the British and the Dutch hypothesis. According to the British hypothesis, presented at the CIBA guest symposium in 1959, the pathogenesis for chronic bronchitis was

based on host and exogenous factors, such as repeated chest infections, air pollution and smoking. According to this hypothesis it was suggested that the exogenous factors caused hypersecretion of mucus which inhibited the host defence, causing repeated acute or chronic respiratory tract infections and eventually to a decline in lung function. In contrast to the British theory, the Dutch hypothesis (DH) proposed that genetically determined host factors (such as genetic predisposition to atopy and bronchial hyperresponsiveness), combined with environmental factors (such as smoking) could predict the hosts response to the exogenous factors.[19]

According to this theory asthma, chronic bronchitis and emphysema are different expressions of a primary abnormality in the airways, and an interaction between genetic predispositions and exogenous factors determine which manifestation a subject develops. In the COPD field this postulated concept of genetically determined host factors provide an explanation as to why subjects exposed to identical exogenous factors (tobacco smoke and environmental pollution [TSEP]), developed different symptoms and manifestations i.e. chronic bronchitis on its own, or in addition to airflow obstruction. According to this hypothesis, asthma and COPD have a single genotype with two phenotypes.

The modern day view concerning the etiology of COPD began with Fletcher and his co-workers, and was later developed by others, and resembles the DH. Fletcher revealed that in susceptible smokers (comparable with the host factors), tobacco smoking is strongly related to chronic bronchitis and

airflow obstruction, and that these were two different diseases. One of the two diseases was chronic bronchitis (CB) without airflow obstruction and the other was airflow obstruction which in some individuals could co-exist with chronic bronchitis. For the first time Fletcher and his colleagues were able to show that tobacco smoking accelerated the decline of FEV_1, and that smoking cessation could halt this rapid decline. It was demonstrated that different populations of smokers, i.e. susceptible and non-susceptible smokers, showed different trends in their lung function decline. Cigarette smoking is recognised as the cause of COPD in the vast majority of patients. Although not fully understood, it is widely accepted that an abnormal inflammatory response of the lungs to noxious particles and gases beyond the normal protective inflammatory response is involved in the development of COPD.[20]

Epidemiology

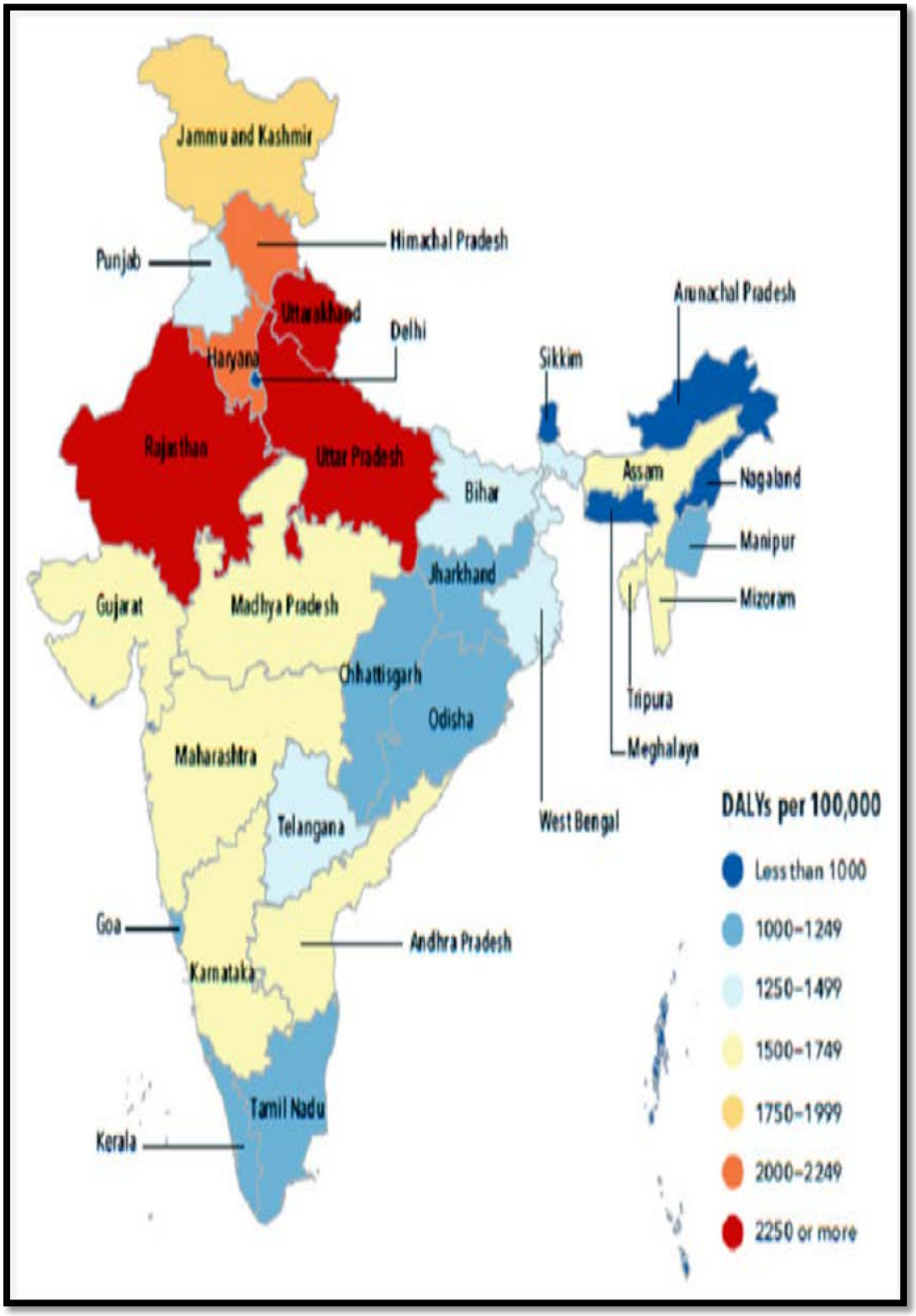
In India, COPD is the second most common lung disorder after pulmonary tuberculosis. It is more commonly encountered in the middle-aged patients and is extremely rare below the age of 35 years. Prevalence of COPD in rural and urban areas is more or less equal.[21] COPD has rapidly advanced globally as one of the most serious health issues. As per WHO estimates, 65 million people have moderate to severe chronic obstructive pulmonary disease. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. It is a well known fact that almost 90% of COPD deaths occur in low- and middle-income countries (LMICs).

At one point in time, COPD was more common in men, but because of increased tobacco use among women in high-income countries and the higher risk of exposure to indoor air pollution (such as biomass fuel used for cooking and heating) in low-income countries, COPD at present affects men and women almost equally. In 2002, COPD was the fifth leading cause of death. As per estimates, in 2020, COPD will attain the third position as the leading cause of death globally.[2]

COPD is more commonly seen in people living in polluted areas as well in those engaged in dusty occupations. Continued exposure to environmental and occupational dusts (EODs) is an important cause of chronic bronchial irritation which may also progress to airway obstruction after prolonged and persistent injury to the airways.[22] COPD is one of the biggest causes of death in India today.

A varied range of prevalence of COPD in different states has been visualized in different studies. Men had a prevalence range of 2 to 22% and women between 1.2 to 19% in different population-based studies pan India. A graphical overview of India as per the disability adjusted life years (DALYs) rate due to COPD is shown in Figure 1.[23]

Figure 1: Geographic distribution of DALYs due to COPD per 100000 population in India



Aetiology

Tobacco smoking

The evidence that tobacco smoking is the most important aetiological factor in COPD is overwhelming. The greater the total tobacco exposure, higher the risk of developing COPD.[24] Hukka and beedi smoking are equally harmful. Pipe and cigar smokers show greater mortality from COPD when compared with non-smokers. The cumulative amount of tobacco smoked is related to its adverse affects.

This is expressed as pack-years and is calculated by multiplying the number of packs (1 pack = 20 cigarettes) with years of smoking. Inhaled smoke in combination with latent host susceptibility and environmental factors produce COPD in 15% of smokers. Long-term cigarette smoking affects ciliary movement, causes hypertrophy and hyperplasia of mucus secreting glands.[25]

Environmental exposures

Certain investigators have reported about increased respiratory symptoms in those living in urban surroundings in comparison to rural surroundings. Increased pollution in the urban settings might be the cause. A concrete relationship between air pollution to chronic airflow obstruction is yet to be proven. Long-term exposure to smoke produced by biomass combustion, a common mode of cooking in some countries also seems to be a risk factor of significance for COPD amidst women in these countries. Ambient air pollution

has a much lesser importance as a risk factor for COPD when compared to cigarette smoking.[26]

Occupation

COPD is frequently observed in persons who are engaged in occupations exposing them to either organic or inorganic dusts or to noxious gases.[27] Occupations including coal mining, gold mining and cotton textile dust, have been suggested as risk factors for chronic airflow obstruction. Exposure to dust from coal mines was a prominent risk factor for emphysema in both smokers and non-smokers.[28]

Socioeconomic status

Socioeconomic status (SES) is one of the most powerful determinants of health across a range of chronic diseases. SES is defined as an individual's social and economic standing and serves as proxy for social or economic position or rank in a social group. More than a measure of income, SES encompasses several other measures including education, occupation, housing, assets, and participation in social organization.

While lower SES was found to be associated with greater COPD morbidity and mortality in HIC, few studies have examined the role of low SES in the prevalence of COPD among LMICs. An understanding of the role of SES and COPD in LMICs will potentially inform public interventions beyond harm reduction, i.e., tobacco cessation and decreased biomass fuel smoke

exposure, toward those aimed at disparities in SES. Factors limiting a comprehensive assessment of the relationship between SES and COPD in LMICs include the high cost of spirometry and limited data from which to analyze associations. Here, we describe the relationship between SES and COPD prevalence among the ten low- and middle-income settings in Argentina, Bangladesh, Chile, Peru, and Uruguay, which encompass a diversity of geographies, ethnicity, and variations in altitude and degree of urbanization.[29]

Respiratory infections

Infections are often the precipitating cause of acute exacerbations of COPD (AECOPD) and contribute significantly to morbidity and mortality. Viral respiratory infections in infancy may cause airways obstruction in later life.

Familial and Genetic Host Factor (FGF)

Alpha-1-antitrypsin (α1-AT) is a protease inhibitor (Pi), acts as an acute phase reactant and a potent inhibitor of serine proteases. The commonest allele in all populations is PiM and the most common phenotype PiMM.[18] The common M allele is associated with normal α1-AT levels. The S allele is associated with slightly reduced α1-AT levels, and the Z allele, associated with markedly reduced α1-AT levels. Severe alpha-1-antitrypsin (α1-AT) deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

Although only approximately 1% to 2% of COPD patients are found to have severe α1-AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Cigarette smokers with severe α1-AT deficiency are more likely to develop COPD at early ages.[30]

Familial aggregation of chronic bronchitis has been well demonstrated. Incidence of α1-AT deficiency in patients presenting with COPD is 1% to 2% but increases to about 50% in patients with severe disease who are under 40 years of age.

Inflammation in COPD

As chronic inflammation is an important process in COPD, pro-inflammatory mediators such as chemokines and cytokines will play an important role in the pathogenesis of COPD. There is now increasing recognition of COPD as a multi-component disease with manifested systemic complications.[31] The disease is not restricted to just the airways, as emphysema and airflow limitation, but can also often present with significant extrapulmonary abnormalities. The identification of these cytokines in the plasma of patients with COPD strongly suggests that the local inflammatory response communicates with the systemic circulation via these mediators.

The local inflammatory process in the lungs may spill over into the systemic circulation to produce systemic changes either by direct effects of released chemokines and cytokines, or indirectly by modification and

activation of peripheral inflammatory cells. The intensity of the inflammatory process correlates with the severity of COPD, and there is also evidence that patients with high values of inflammatory markers when stable had a more rapid decline of lung function over time.[32]

Body Mass Index (BMI)

Data from the Copenhagen City Heart Study (CCHS) showed that the severity of COPD tended to be greater in patients with low BMI (with low BMI defined as a BMI less than 20 kg/m^2). In subjects with mild airflow limitation (FEV1>70% of predicted value) 3.5% of males and 12.5% of females also had low BMI. Studies have also shown that loss of skeletal muscle may also occur in COPD patients with normal weight.[33] Weight loss in patients with COPD was an independent risk factor shown to increase the risk of exacerbations and all-cause mortality, independent of the degree of airflow limitation.[34-39] Weight gain on the other hand, seemed to have a protective effect in normal and underweight patients with severe COPD.

Pathogenesis of COPD

Emphysema and chronic bronchitis often are clinically grouped together under the heading of chronic obstructive pulmonary disease (COPD) because of their propensity to coexist. The commonest form of COPD is the combination of chronic bronchitis and pulmonary emphysema. Chronic bronchitis, however, does not always lead to emphysema nor do all cases of emphysema have changes of chronic bronchitis. The association of the two

conditions is principally linked to the common etiologic factors-most importantly tobacco smoke and air pollutants.

The definition of emphysema is morphologic, whereas chronic bronchitis is defined on the basis of clinical features such as the presence of chronic and recurrent cough with excessive mucus secretion. The anatomic distribution is partially different; chronic bronchitis initially involves the large airways, whereas emphysema affects the acinus.[40]

Emphysema

The WHO has defined pulmonary emphysema as combination of permanent dilatation of air spaces distal to the terminal bronchioles and the destruction of the walls of dilated air spaces. Emphysema is characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls without significant fibrosis.

Classification of pulmonary emphysema as per WHO definition based on the portion of the acinus involved:

1. Centriacinar (centrilobular) emphysema
2. Panacinar (panlobular) emphysema
3. Paraseptal (distal acinar) emphysema
4. Irregular (para-cicatricial) emphysema

5. Mixed (unclassified) emphysema.[23]

1. Centriacinar (Centrilobular) emphysema

The distinctive feature of centriacinar (centrilobular) emphysema is the pattern of involvement of the lobules: The central or proximal parts of the acini, formed by respiratory bronchioles, are affected, while distal alveoli are spared. This type of emphysema is most commonly seen as a consequence of cigarette smoking in people who do not have congenital deficiency of α1-antitrypsin.

2. Panacinar (Panlobular) emphysema

In panacinar (panlobular) emphysema, the acini are uniformly enlarged, from the level of the respiratory bronchiole to the terminal blind alveoli. In contrast with centriacinar emphysema, panacinar emphysema tends to occur more commonly in the lower lung zones and is the type of emphysema that occurs in α1-antitrypsin deficiency.

3. Distal Acinar (Paraseptal) emphysema

In distal acinar (paraseptal) emphysema, the proximal portion of the acinus is normal but the distal part is primarily involved. The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins.

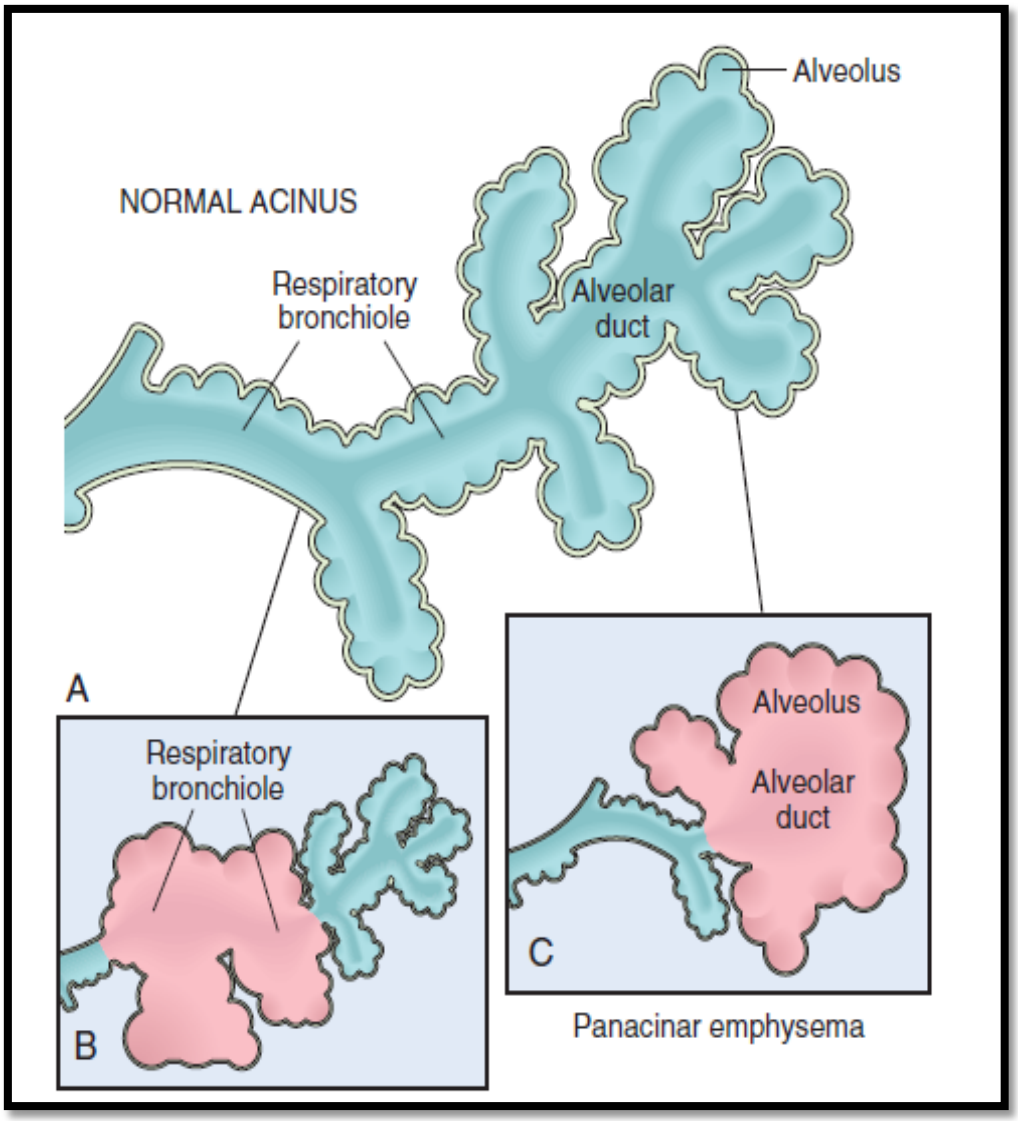
4. Irregular emphysema

Irregular emphysema, so named because the acinus is irregularly involved, is almost invariably associated with scarring, such as that resulting from healed inflammatory diseases.

5. Mixed (Unclassified) emphysema

The same lung may show more than one type of emphysema. It is usually due to more severe involvement resulting in loss of clear-cut distinction between one type of emphysema and the other.

Figure 2: Major patterns of emphysema

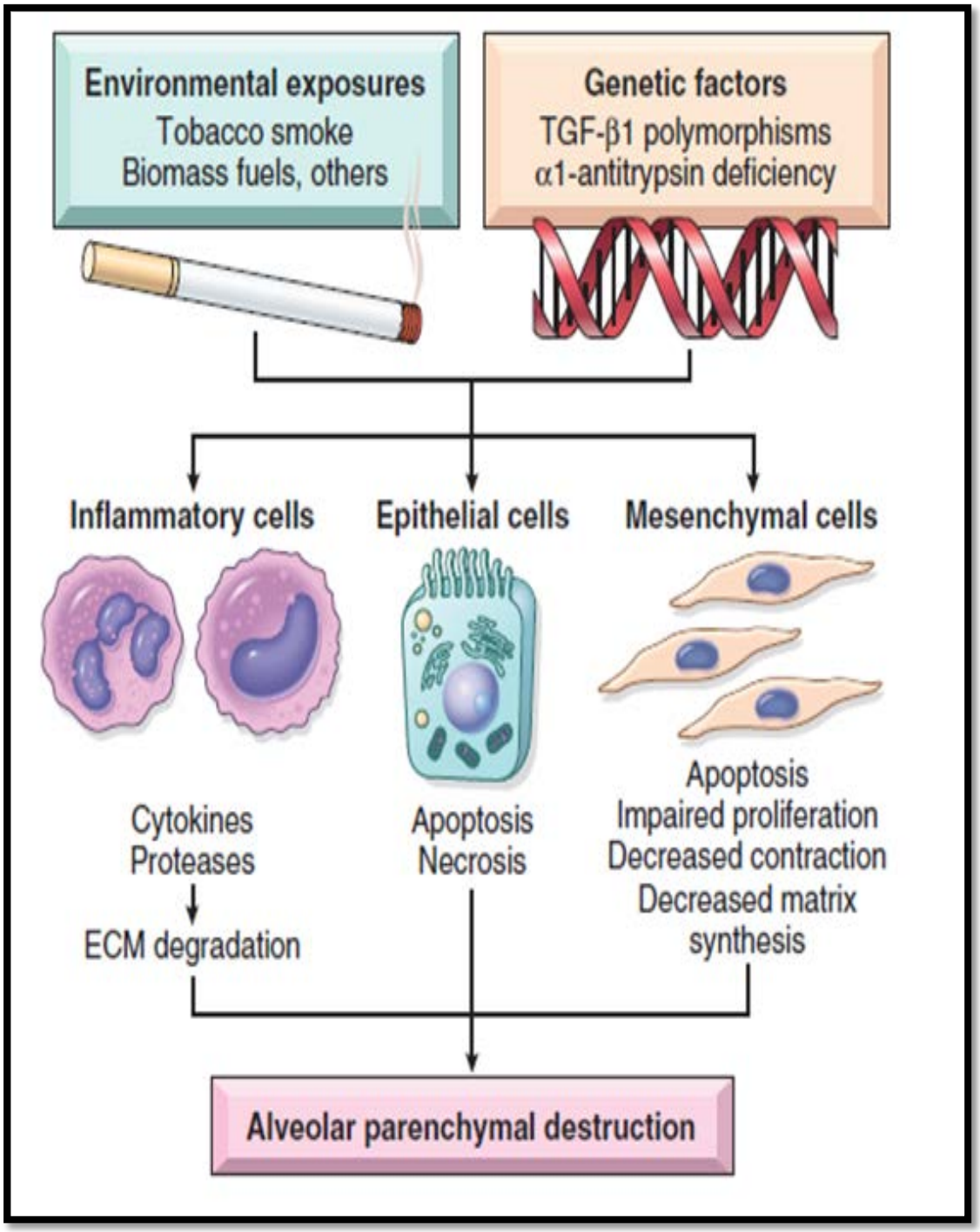


A. Diagram of normal structure of the acinus, the fundamental unit of the lung.

B. Centriacinar emphysema with dilation that initially affects the respiratory bronchioles.

C. Panacinar emphysema with initial distention of all the peripheral structures

Figure 3: Pathogenesis of Emphysema



Loss of cellular homeostasis in emphysema pathogenesis. Exposure to inhaled toxins (such as cigarette smoke) leads to epithelial cell death, inflammation, and extracellular matrix proteolysis.

Chronic bronchitis

Chronic bronchitis (CB) is defined clinically as persistent cough with expectoration on most days for at least three months of the year for two or more consecutive years. It is more common in middle-aged males than females; about 20% of adult men and 5% of adult women on an average have chronic bronchitis, but only very few of them progress to serious disabling COPD.

Etiopathogenesis

The two most important etiologic factors responsible for majority of cases of chronic bronchitis are cigarette smoking and atmospheric pollution. Other factors are occupation, infection, familial and genetic factors.

Smoking

Heavy smoking is the most identified factor implicated to cause chronic bronchitis and emphysema. The propensity of heavy cigarette smokers to develop chronic bronchitis is 4 to 10 times higher.

Long term cigarette smoking appears to cause actions on the lungs in these ways:

i. Impairment of ciliary movement.

ii. Preventing the function of alveolar macrophages.

iii. Hypertrophy and hyperplasia of mucus secreting glands.

iv. Obstruction of small airways.

v. Vagal stimulation leading to bronchoconstriction.

Atmospheric pollution

Industrialised urban areas have a higher incidence of chronic bronchitis as a result of atmospheric pollutants. Sulfur dioxide, nitrogen dioxide, particulate dust and toxic fumes are some of the atmospheric pollutants which increase the risk of developing chronic bronchitis.

Occupation

Workers engaged in certain occupations such as in cotton mills (byssinosis), plastic factories etc. are exposed to various organic or inorganic dusts which contribute to disabling chronic bronchitis in such individuals. Sputum production is generally observed in patients with chronic bronchitis. In patients with byssinosis the sputum will be brownish- black color.

Infection

Bacterial, viral and mycoplasmal infections do not initiate chronic bronchitis but usually occur secondary to bronchitis. Cigarette smoke, however, predisposes to infection responsible for acute exacerbation in chronic bronchitis.

Familial and genetic factors (FGF)

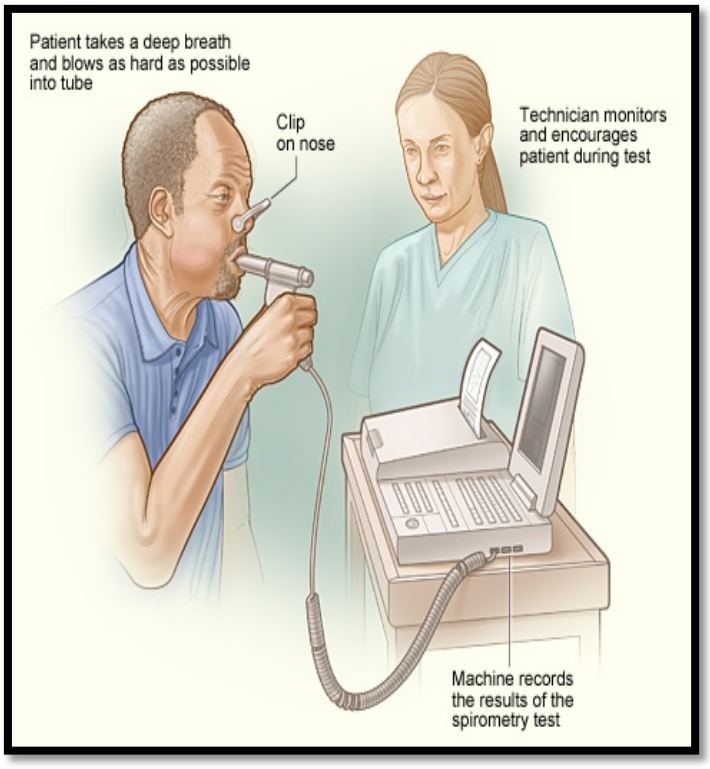
There appears to be a poorly-defined familial tendency and genetic predisposition to develop disabling chronic bronchitis. However, it is more likely that non-smoker family members who remain in the air-pollution of home are significantly exposed to smoke (passive smoking) and hence have increased blood levels of carbon monoxide.[41,42]

Diagnosis

COPD must be considered in patients with dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors for COPD. Diagnosis is made using spirometry. Post-bronchodilator $FEV_1/FVC<0.70$ substantiates that there is persistent airflow limitation and therefore of COPD in patients with appropriate symptoms and prominent exposures to noxious stimuli. Spirometry is the most reproducible and objective measurement of airflow limitation. It is a noninvasive and readily available test.

The weak specificity of peak expiratory flow measurement renders it unreliable to be used alone as the only diagnostic test in COPD in spite of its good sensitivity.[43]

Figure 4: Spirometer and spirometry for COPD diagnosis



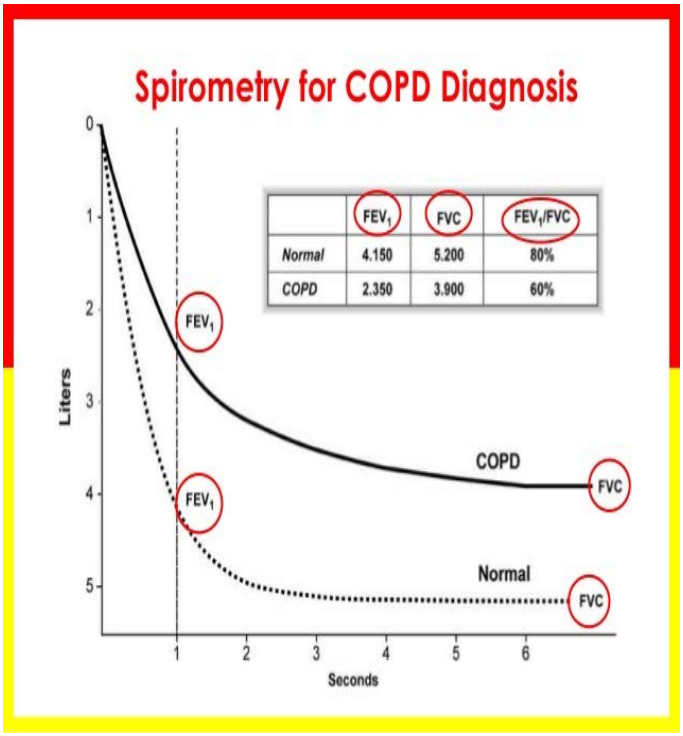


Table 1: Key indicators for considering a diagnosis of COPD[17]

Indicators	
Dyspnoea that is	Progressive over time Characteristically worse with exercise Persistent
Chronic cough	May be intermittent and may be unproductive Recurrent wheeze
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
Recurrent lower respiratory tract infections	
History of risk factors	Host factors (such as genetic factors, congenital/developmental abnormalities etc) Tobacco smoke (including popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapours, fumes, gases and other chemicals
Family history of COPD and/or childhood factors	For example low birth weight, childhood respiratory infections

Differential diagnosis[44]

A major differential diagnosis is bronchial asthma. In some patients with chronic bronchial asthma, a clear distinction from COPD is not possible using

current imaging and physiological testing techniques. Current management is similar to that of bronchial asthma.

Table 2: Differential diagnosis of COPD

Diagnosis	Suggestive features
COPD	Onset in mid-life Symptoms slowly progressive History of tobacco smoking or exposure to other types of smoke
Bronchial asthma	Onset early in life (often childhood) Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis and/or eczema also present Family history of asthma Obesity coexistence
Congestive heart failure	Chest x-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow limitation
Bronchiectasis	Large volumes of purulent sputum Three layered sputum Commonly associated with bacterial infection Chest x-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages

	Chest x-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset at younger age, non-smokers May have history of rheumatoid arthritis or acute fume exposure Seen after lung or bone marrow transplantation CT on expiration shows hypodense areas
Diffuse panbronchiolitis	Predominantly seen in patients of Asian descent Most patients are male and non-smokers Almost all have chronic sinusitis Chest x-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation

Alpha-1 Antitrypsin deficiency (AATD) screening[17]

The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.

Assessment[45]

The goals of COPD assessment are to determine the severity of airflow limitation, its impact on the patient's health status and the risk of future events in order to eventually guide therapy.

COPD assessment must consider the following aspects of the disease separately in order to achieve this:

- The presence and severity of the spirometric abnormality
- Current nature and magnitude of the patient's symptoms
- Exacerbation history and future risk
- Presence of comorbidities

Classification of severity of airflow obstruction

Specific spirometric cut-points are used for purposes of simplicity. Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimize variability.

Table 3: Classification of airflow limitation severity in COPD based on post bronchodilator FEV_1 (In patients with $FEV_1/FVC < 0.70$)

GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

There is only a weak correlation between FEV_1, symptoms and impairment of a patient's health status.

Assessment of symptoms

In the past, COPD was viewed as a disease largely characterized by breathlessness. However, it is now recognized that COPD affects patients beyond just dyspnoea.

Revised combined COPD assessment

The "ABCD" assessment tool of the 2011 GOLD update was a major advancement from the simple spirometric grading system of the earlier versions of GOLD because it incorporated patient-reported outcomes and highlighted the importance of exacerbation prevention in the management of COPD.

Management of COPD[46]

An effective COPD management plan includes four components:

1. Assess and Monitor Disease
2. Reduce Risk Factors
3. Manage Stable COPD
4. Manage Exacerbations.

Management of Mild to Moderate COPD (Stages I and II) involves preventing disease progression by avoiding risk factors and using

pharmacotherapy when needed to control symptoms. Severe (Stage III) and Very Severe (Stage IV) COPD often requires integrating multiple disciplines, a number of treatment approaches, and the clinician's undying commitment to support the patient as the disease progresses.

COPD patients may require specific counselling about smoking cessation, instruction in physical exercise, nutritional advice and continued nursing support.

Goals of COPD management

- Relieve symptoms
- Prevent disease progression
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

Non-pharmacological management of COPD

Optimum management of COPD requires non-pharmacological interventions combined with pharmacological treatment.

Non-pharmacological management options for COPD include

i. Smoking cessation

ii. Pulmonary rehabilitation

iii. Pneumococcus and influenza vaccinations

iv. Non-invasive positive pressure ventilation (NPPV)

v. Long-term oxygen therapy (LTOT)

vi. Surgery and bronchoscopic lung volume reduction

Smoking cessation

Smoking cessation remains the only proven intervention to slow the decline of lung function and should be prioritized in the management of COPD patients. As smoking is the most important modifiable risk factor for COPD, quitting smoking is critical to reduce the occurrence and progression of the disease.[47] All patients with COPD should be strongly urged to quit smoking and educated about the benefits of quitting.

Pulmonary rehabilitation

In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnoea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6-12 month period.

Pneumococcus and influenza vaccinations

Patients with COPD should receive the influenza vaccine annually. Polyvalent pneumococcal vaccine is also recommended.[36] Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all elderly patients.[17] PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in COPD patients < 65 years, with an FEV1 < 40% predicted.

Non-Invasive Positive Pressure Ventilation (NPPV)

The aim of delivering NPPV via nasal or facial mask is to improve hypoventilation and provide rest to the respiratory muscles in COPD patients. NPPV improves the outcome in severe exacerbations of COPD complicated by hypercapnia and respiratory acidosis. Clear benefits are observed in patients with COPD and coexisting obstructive sleep apnoea or obesity hypoventilation.[48]

Long-Term Oxygen Therapy (LTOT)

Supplemental O_2 is commonly prescribed for patients with exertional hypoxemia or nocturnal hypoxemia. Supplemental O_2 is the only pharmacologic therapy demonstrated to unequivocally decrease mortality rates in patients with COPD.[36]

Surgery and Bronchoscopic Lung Volume Reduction (SBLVR)

Surgical options for COPD include LVRS, bullectomy and lung transplantation.

Lung Volume Reduction Surgery (LVRS)

LVRS involves the surgical reduction of lung volume, with multiple excisions improving elastic recoil and reducing hyperinflation. It is beneficial in selected COPD patients with upper-lobe emphysema.

Bullectomy

Bullectomy involves removal of one or more large bullae that do not contribute to gas exchange, decompressing the adjacent lung parenchyma and improving ventilation.[49]

Lung transplantation

COPD is currently the second leading indication for lung transplantation.

Current recommendations are that candidates for lung transplantation should have severe disability despite maximal medical therapy and be free of comorbid conditions such as liver, renal, or cardiac disease.[36]

Pharmacological management of COPD

The aim of pharmacologic therapy for COPD is to reduce symptoms, reduce the frequency and severity of exacerbations, improve exercise tolerance and health status. Presently, there is no conclusive clinical trial evidence that any currently available medications for COPD modify the long-term decline in lung function.

Bronchodilators

Bronchodilators are medications that increase FEV_1 and/or change other spirometric variables.[44]

Three main classes of bronchodilator are in current clinical use:

Beta2 Adrenergic agonists (sympathomimetics)

Theophylline (a methylxanthine)

Anticholinergic agents (muscarinic receptor antagonists)[50]

Beta2 Adrenergic agonists (sympathomimetics)

- The principal action of beta2-agonists is stimulation of beta2-adrenergic receptors, which increases cyclic AMP, relax airway smooth muscle and reduces bronchoconstriction.

- There are short-acting (SABA) and long-acting (LABA) beta2-agonists. Short-acting inhaled beta2-agonists such as salbutamol, levosalbutamol, terbutaline, and fenoterol have a relatively rapid onset of bronchodilator effect, which usually wears off within 4–6 hours.

- Formoterol and salmeterol are twice-daily LABAs that significantly improve FEV_1 and lung volumes, dyspnoea, health status, exacerbation rate and number of hospitalizations. Salmeterol and formoterol are formulated for twice-daily dosing, have duration of effect of 12 hours or

more with no loss of effectiveness overnight or with regular use in COPD patients.

- Indacaterol, a novel beta2-agonist is approved by both the EMA and the FDA for the treatment of COPD. Indacaterol is a once daily LABA that improves breathlessness, health status and exacerbation rate.

- Oladaterol and vilanterol are additional once daily LABAs that improve lung function and symptoms.

Once-daily inhaled beta2 agonists are useful in patients with COPD and may have additive effects with LAMAs.[49]

Side effects of beta2 agonists

- Muscle tremor (direct effect on skeletal muscle β2 receptors)
- Tachycardia (direct effect on atrial beta2 receptors, reflex effect from increased peripheral vasodilation via β2 receptors)
- Hypokalemia (direct β2 effect on skeletal muscle uptake of K+)
- Restlessness
- Hypoxemia (↑ $\dot{V}/\dot{Q}$ mismatch due to reversal of hypoxic pulmonary vasoconstriction)
- Metabolic effects (↑ FFA, glucose, lactate, pyruvate, insulin)

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle. Short-acting antimuscarinics (SAMAs) are ipratropium and oxitropium. Long acting antimuscarinic antagonists (LAMAs) are tiotropium, aclidinium, glycopyrronium bromide and umeclidinium.[44] Ipratropium is probably the most frequently used short-acting anticholinergic drug at present.

The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting beta2 agonists. Tiotropium has been formulated for once-daily dosing, providing 24-hour bronchodilation, and has a selectivity for M1 and M3 receptors. Treatment with tiotropium has shown symptom improvement, decreased hyperinflation, reduced dyspnoea, and improved quality of life. Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.[44]

In COPD, anticholinergic drugs may be as effective as or even superior to beta 2 agonists. Anticholinergic drugs reduce air trapping and improve exercise tolerance in patients with COPD.

Short-Acting Antimuscarinics (SAMA)

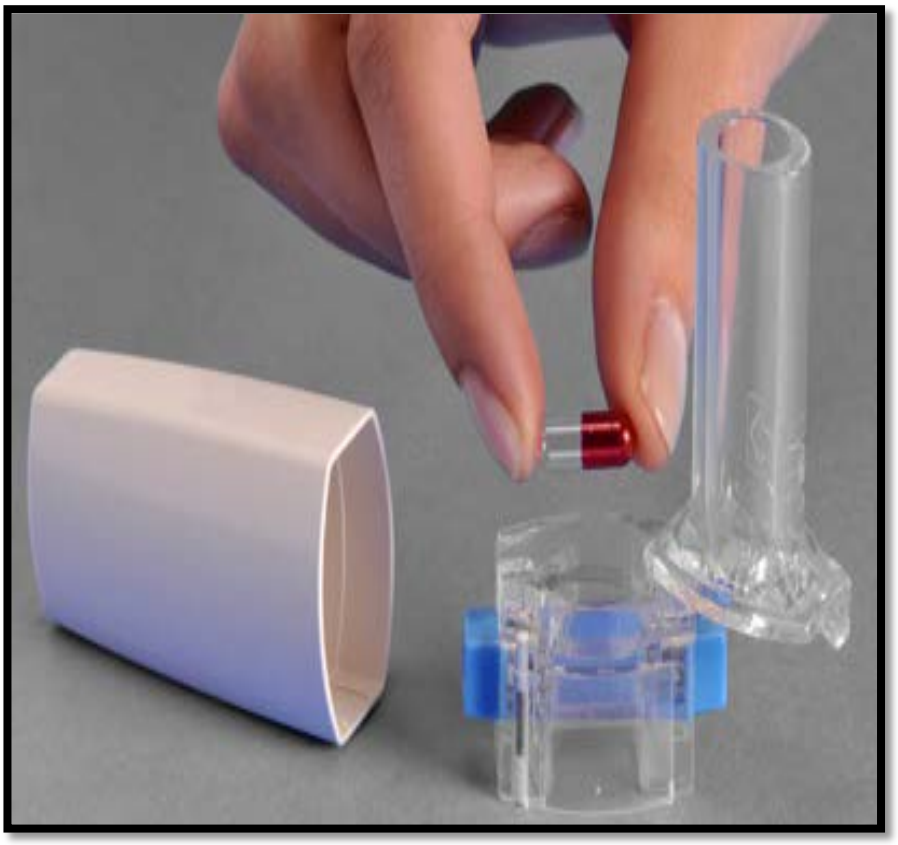
Ipratropium bromide is available as a pMDI and nebulized preparation. It has relatively slow onset of bronchodilation and is usually maximal 30-60 min after inhalation but may last for 6-8 h. Preferably given by MDI three or

four times daily on a regular basis, rather than intermittently for symptom relief. LAMAs, like tiotropium bromide has replaced ipratropium bromide to a large extent.

Long-Acting Muscarinic Antagonists (LAMAs)

LAMAs have now been developed for the treatment of COPD. Tiotropium bromide is a long-acting anticholinergic drug that is suitable for once-daily dosing as a DPI or via a soft mist mini nebulizer device.

Figure 5: Dry powder inhaler



It was more effective than ipratropium four times daily in several studies; it also significantly reduces exacerbations. Over a 4-year period,

tiotropium displayed no effect on disease progression, but there was a positive impact in the functioning of the lung and health status and diminishment in exacerbations and all-cause mortality.

Glycopyrronium bromide and umeclidinium bromide are also once-daily LAMAs with very similar clinical effects to tiotropium. Aclidinium bromide has to be given twice daily. LAMAs are now becoming the bronchodilators of choice for patients with COPD.

Side effects of antimuscarinic agents

Inhaled anticholinergic drugs are generally well tolerated. LAMAs cause dryness of the mouth in 10%–15% of patients, but this usually disappears during continued therapy. Urinary retention is occasionally seen in elderly patients.[48]

Methylxanthines

A methylxanthine is a competitive, nonselective phosphodiesterase inhibitor that increases the intracellular cAMP level and activation of protein kinase A, resulting in smooth muscle relaxation and bronchodilation.[49] Theophylline is the most commonly used methylxanthine. It is metabolized by cytochrome P450 mixed function oxidases. Combining theophylline with salmeterol brings about an increased improvement in FEV_1 and breathlessness than salmeterol alone.[44]

Theophylline is still used as a bronchodilator in COPD, but inhaled anticholinergics and beta2 agonists are preferred. Theophylline tends to be added to these inhaled bronchodilators in patients with more severe disease and has been shown to give additional clinical improvement when added to a LABA.

Table 4: Side effects of theophylline[45]

Side effect	Proposed mechanism
Nausea and vomiting	PDE4 inhibition
Headaches	PDE4 inhibition
Gastric discomfort	PDE4 inhibition
Diuresis	A1 receptor antagonism
Cardiac arrhythmias	PDE3 inhibition, A1 receptor antagonism
Epileptic seizures	A1 receptor antagonism

Combination bronchodilator therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator. Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV_1 and symptoms. Treatment with

formoterol and tiotropium in separate inhalers has a bigger impact on FEV_1 than either component alone. COPD patients whose symptoms are not well-controlled with a single long-acting bronchodilator, another type of long acting bronchodilator is additionally prescribed.[50]

COPD patients who are treated at a lower dose of a LABA/LAMA combination two times a day have shown improvement in symptoms and health status.[51] SABA/SAMA combinations, such as salbutamol/ipratropium, are popular. LABA/LAMA dual combination inhalers indacaterol/glycopyrronium, vilanterol/umeclidinium bromide, olodaterol/tiotropium bromide are all used once daily, whereas formoterol/glycopyrronium bromide, formoterol/ aclidinium bromide are used twice daily. Beneficial effects on lung function are evidenced with these combination drugs in comparison with either LABA or LAMA alone.[52-54]

Inhaled corticosteroids (ICS)

In patients with moderate to very severe COPD and exacerbations, an ICS combined with a LABA is more effective than either component alone in improving lung function, health status and reducing exacerbations. ICSs have no effect on the progression of COPD, even when given to patients with presymptomatic disease. ICSs have no effect on mortality. ICSs reduce the number of exacerbations in patients with severe COPD (FEV_1 < 50% predicted) who have frequent exacerbations and are recommended in these patients. In the ISOLDE study, fluticasone treatment significantly reduced the

number of exacerbations and slowed the loss of quality of life in patients with advanced COPD (FEV_1 <50% predicted). Regular treatment with inhaled corticosteroids should only be considered for symptomatic patients with advanced COPD suffering from repeated exacerbations.[55]

Triple inhaled therapy

Triple therapy involves the addition of a LAMA to LABA/ICS combination therapy for the treatment of COPD. Studies which included patients suffering from severe or very severe COPD, who had greater than one exacerbation of COPD per year have shown lesser number of hospitalizations and COPD exacerbation with LABA/ICS/LAMA triple therapy. Improvement in symptoms, pulmonary function, and quality of life scores were noticed with triple therapy when compared with LABA/ICS combination therapy and with LAMA monotherapy.

A systematic review which compared triple therapy vs. LABA/ICS combination therapy or tiotropium alone reported improvement in pulmonary function and health-related quality of life for the group treated with triple therapy. The safety profile of triple therapy was similar to that of other treatment options available.

Oral glucocorticoids

The multiple side effects of oral glucocorticoids like steroid myopathy that can cause muscle weakness, reduced functionality, and respiratory failure

in patients with very severe COPD. The management of acute exacerbations require oral glucocorticoids, but in chronic daily treatment in COPD the benefits do not outweigh the high rate of systemic complications.[44]

Phosphodiesterase-4 (PDE4) inhibitors

Roflumilast is a selective phosphodiesterase-4 (PDE4) inhibitor and acts by blocking this enzyme activity, increasing intracellular levels of cAMP, which results in reduction of cellular inflammatory activity. Roflumilast is indicated for the treatment of patients with severe or very severe COPD (FEV_1 < 50% of predicted) who continue to have COPD exacerbations, cough and sputum despite maximal inhaled therapy. The recommended dose is 500 μg/day orally once daily.

Side effects of PDE4

- Nausea
- Reduced appetite
- Weight loss
- Abdominal pain
- Diarrhoea
- Sleep disturbance
- Headache[44]

Antibiotics

The indication for prophylactic antibiotics in COPD should be determined on a case-by-case basis. Prophylactic antibiotics are a third-line therapy for the treatment of exacerbators. The available evidence lends support to the use of Azithromycin 250 mg daily or Azithromycin 500 mg three times a week or the use of Erythromycin 500 mg twice daily for 1 year in patients with severe or very severe COPD and in exacerbators despite usual pharmacological treatment. Long-term use is associated with an increased risk of adverse events and development of bacterial resistance.

Table 5: Main drugs for the treatment of COPD[55]

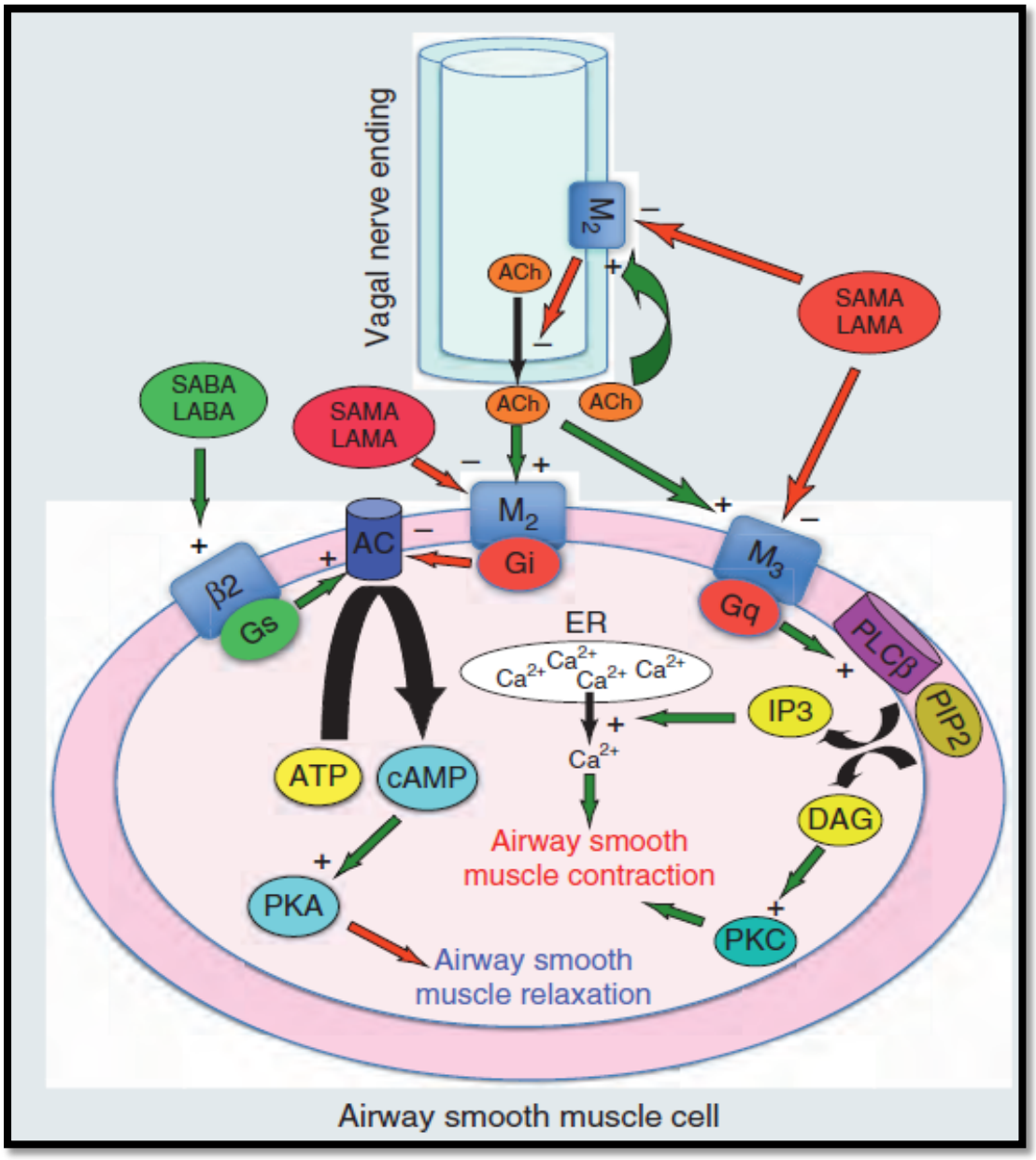
Drug	Dose, µg (except where otherwise indicated)	Duration of action, hours
Short-acting beta2 agonist		
Fenoterol	MDI 100 and 200	4-6
Albuterol (Salbutamol)	MDI 100, 120, 200	4 to 6, 12
Long-acting beta2 agonist		
Formoterol	DPI 12	12
Salmeterol	MDI 25 and DPI 50	12
Indacaterol	DPI 150 and 300	24
Olodaterol	SMI 2.5	24
Short-acting anticholinergic		
Ipratropium (bromide)	MDI 20-40	6-8

Long-acting anticholinergic		
Glycopyrronium (bromide)	DPI 50	12 to 24
Tiotropium	SMI 2.5	24
Umeclidinium (bromide)	DPI 62.5	24
Beta2 agonist plus short-acting anticholinergic		
Fenoterol/ipratropium	MDI 50/20	6 to 8
Salbutamol/ipratropium	MDI 120/20	6 to 8
Beta2 agonist plus long-acting anticholinergic		
Formoterol/aclidinium	DPI 12/400	12
Formoterol/glycopyrronium	MDI 9.6/14.4	12
Indacaterol/glycopyrronium	DPI 110/50	12 to 24
Vilanterol/umeclidinium	DPI 25/62.5	24
Olodaterol/tiotropium	SMI 2.5/2.5	24
Long-acting beta2 agonist plus inhaled corticosteroid		
Formoterol/beclomethasone	MDI and DPI 6/100	12
Formoterol/budesonide	DPI 6/200, 12/400, and 12/200 MDI 6/200	12
Formoterol/mometasone	MDI 5/50, 5/100, and 5/200	12
Salmeterol/fluticasone	DPI 5/100, 50/250, and 50/500	12
	MDI 25/50, 25/125, and 25/250	
Vilanterol/fluticasone	DPI 25/100	24

Phosphodiesterase-4 inhibitor		
Roflumilast	Tablet, 500 mg	24
Macrolide		
Azithromycin	Tablet, 250 and 500 mg	24
Mucolytic		
N-acetylcysteine	Powder, 200 and 600 mg; syrup, 30 mg/mL; and tablet, 600 mg	8 to 12

(MDI: metered dose inhaler; DPI: dry powder inhaler; and SMI: soft mist inhaler)

Figure 6: Mechanism of action of bronchodilators



Pharmacological modulation of airway smooth muscle cell and mechanism of action of bronchodilators. Activating or facilitating effects are shown by green arrows; inhibitory or antagonistic effects are shown by red arrows.[55]

Drug utilization study (DUS)

Studies on drug utilization are a potential tool to evaluate healthcare systems. Data and evidence that are obtained from the period of pre marketing and post marketing are used as a reference to prescribe drugs in clinical practice. The leaps and bounds improvement in the marketing of new drugs, contrast in drug prescribing pattern, delayed adverse effects and the price of drug have enhanced the significance of DUS.

The primary focus of DUS is to imply prescription of drug in an optimal dose for the proper indication with the precise information and at a cost which is affordable, thereby facilitating rational use of drugs in a population. DUS contribute to rational drug use by improving our knowledge and understanding of drug use, and provide early signals of irrational use of drugs thereby helping us to intervene in a timely fashion to improve drug therapy.

Definition

"Drug utilization is defined as the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences."

WHO prescribing indicators

- The total number of drugs prescribed on an average per prescription - measure the extent of polypharmacy

- Percentage of medicines prescribed by generic name
- Percentage of drugs prescribed from essential drug list
- Percentage of prescription with an antibiotic prescribed
- Percentage of prescriptions with injections - measure the overall level of injection use. Propensity to overuse injections is very common

Complementary indicators

- Average drug cost per visit
- Percentage of medicine cost spent on injection

Normal values

- Average number of drug per visit 2-3
- Percentage of visit with an injection prescribed 16-20%
- Percentage of generic drugs prescribed - 100%
- Percentage of drugs prescribed from Essential Drug List 80-100%
- Percentage of visit with antibiotics prescribed should not exceed 40%

Factors influencing drug utilization[55]

1. Population related factor: change in total population, change in population demographic, change in health status of a population
2. System related factor: change and transition associated with health system reform and restructuring changes in policies and programmes
3. Research and technology related: new treatment approach
4. Pharmaceutical industry: development of new drug product, promotion of drugs to physician, drug sampling, direct to consumer advertising
5. Practice and people related: change in prescribing and dispensing practice

Uses of DUS

i. Facilitate rational use of drug

ii. Increase our understanding of how drugs are being used

iii. Generate hypothesis that set the agenda for further investigation and thus avoid prolonged irrational use of drugs

iv. Assess whether interventions intended to improve drug use have had the desired impact

v. By comparing data from different localities may identify and promotion of best practice

Pharmacovigilance

Pharmacovigilance is an important post-marketing tool in ensuring the safety of pharmaceutical product. It involves evaluating information gathered from the health care providers, pharmaceutical company and patients in order to understand the risks and benefits of a particular drug.

These activities

- Identify new information about adverse effects of the drug
- Prevent harm to the patient

Major role of pharmacovigilance is to identify and evaluate safety signals. Safety signal refers to concern about an excess of adverse events compared to that would be expected with a product use.

Definition

Pharmacovigilance[52]

"Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects particularly long term and short term side effects of medicines."

Adverse Event (AE)

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment is called as AE.

Adverse Drug Reaction (ADR)[53]

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional. Any response to a medicinal product which is noxious and unintended is ADR.

Serious adverse event or serious adverse drug reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death or is life threatening. Life threatening refers to an event in which patient was at risk of death at the onset of event like:

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability
- Congenital anomaly or birth defect

Objectives

The main objectives of National Pharmacovigilance Programme are as following

- To foster the culture of Adverse Event notification and reporting
- To establish a viable and broad based ADR monitoring programmes in India
- To create an ADR database for the Indian population
- To create awareness of ADR monitoring among people
- To ensure optimum safety of drug products in Indian market
- To create infrastructure for ongoing regulatory review of Periodic Safety Updates Regulators (PSURs)
- To promote rational and safe use of medicines.
- To contribute the knowledge of value, detriment, efficiency and hazard of medicines.
- To encourage edification and clinical training.
- To endorse healthy communication to the community.
- To increase public protection from the new products.

Clinical importance

New drug released into market lack long term safety data. Prescribed drugs response varies due to interactions with drug and food. Awareness about pharmacovigilance and practice according to it has a large impact on health care quality. Information on clinical, pathological and epidemiological information related to adverse reaction help us to fully understand adverse effects of drugs and for identifying patients at risk. ADR have the potential to provide insight into structure-activity relationship, pharmacokinetic, pharmacodynamic and genetic factors affecting the action of drugs. This may provide lead for other novel indications of the drug. Knowledge acquired following stringent monitoring on adverse effect of drug can prevent unnecessary suffering by patients and decrease financial loss of the patient due to inappropriate use of drug.

AIMS AND OBJECTIVES

Aim: To evaluate pattern of drug use and study the safety profile of drugs used in the management of COPD.

Objectives:

1. To determine the utilization of drugs in General Medicine OPD for the management of COPD using WHO Drug use indicators.
2. To analyze the prescribing trends of drugs for management of COPD in General Medicine OPD.
3. To assess safety profile.

METHODOLOGY

Materials and methods

Study design

This study was a prospective cross sectional observational study.

Study setting

This study was conducted in the Outpatient Department, Department of General Medicine, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari District, Tamil Nadu.

Study Period

This study was done during the period January 2017-January 2018.

Inclusion criteria

- Patients diagnosed with COPD and on treatment.
- Age group of 40 to 70 years of both genders.
- Subjects willing to give informed consent were included in the study.

Exclusion criteria

- Patients with acute exacerbation of COPD.

- Patients taking medications for other co-morbid conditions like diabetes mellitus, hypertension, and hyperlipidemia.

Institutional Human Ethics Committee Approval

Ethical clearance was obtained from Institutional Human Ethics Committee (IHEC) Ref. No: **SMIMS/IHEC No: 1/ Protocol no: 25/2016 (Appendix I)**

Study procedure

The study was carried out after getting approval from Institutional Human Ethics Committee (IHEC). Patients who come to General Medicine OPD satisfying inclusion and exclusion criteria were enrolled in the study. They were explained about the study and written informed consent (Appendix II) was obtained from each patient or their attender before recruiting them into the study. Details from the prescriptions in the case file were recorded from (Appendix III). The demographic data of the patients, presenting complaints, details of drugs used and adverse effect of drugs were recorded. Details of drugs included dose, route and frequency of medication.

Assessment of drug use indicators

Following drugs use indicators were assessed according to WHO guidelines.

Prescribing Indicators

a) Average number of drugs per patient

$$\frac{\text{Total number of different drugs prescribed}}{\text{Number of patients surveyed}}$$

b) Percentage of drugs prescribed by generic name

$$\frac{\text{Number of drugs prescribed by generic name}}{\text{Total number of drug prescribed}} \times 100$$

c) Percentage of patients with injection prescribed

$$\frac{\text{Number of patients with injection prescribed}}{\text{Total number of drug prescribed}} \times 100$$

d) Percentage of patients with inhaler use

$$\frac{\text{Number of patients with inhaler use}}{\text{Total number of patients}} \times 100$$

e) Percentage of patients with oral prescribed

$$\frac{\text{Number of patients with oral prescribed}}{\text{Total number of drug prescribed}} \times 100$$

f) Percentage of patients with nebulization

$$\frac{\text{Number of patients with nebulization}}{\text{Total number of patients}} \times 100$$

g) Percentage of drugs prescribed from Essential drug list (EDL)

$$\frac{\text{Number of drugs prescribed from EDL}}{\text{Total number of drugs prescribed}} \times 100$$

The data collected was compared with WHO values given below,

- Average number of drugs per patient 2-3.
- Percentage of patients with an injection prescribed 16-20 %.
- Percentage of drugs prescribed by generic name- 100%.
- Percentage of drugs prescribed from EDL 80-100%.

Essential Drugs from National List of essential medicine (2017) India.[54]

Prescribing pattern of drugs was evaluated by

- Average number of drugs and maximum number of drugs prescribed for each patient.
- Percentage of patients on monotherapy or combination of drugs in COPD.

- Utilization of various classes of drugs in COPD.
- Order and frequency in the utilization of drugs in COPD.
- Adverse effects related to treatment with drugs for COPD.

Safety profile was assessed using WHO causality assessment.

Analysis of data

The data collected were entered into Microsoft Excel and subsequently analyzed. Descriptive statistics was used for data analysis.

OBSERVATIONS AND RESULTS

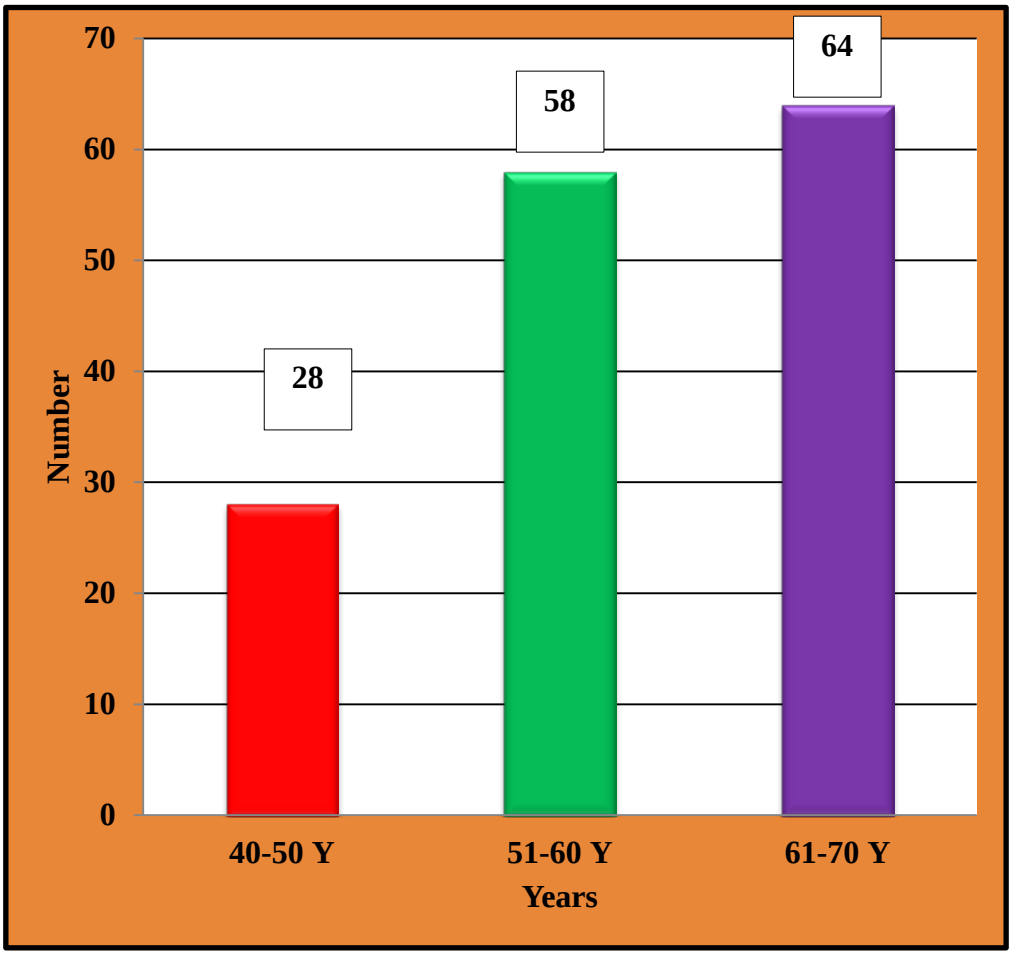
Prospective evaluation of prescriptions of 150 patients who attended General Medicine OPD in Sree Mookambika Institute of Medical Sciences between January 2017 and January 2018 was done and the data were analyzed.

Baseline demographic data

Table 6: Age distribution of patients

Age (years)	Number	Percentage (%)
40-50 years	28	18.67
51-60 years	58	38.67
61-70 years	64	42.66
Total	**150**	**100.00**

Figure 7: Age wise distribution of patients



The study population ranged from age 40-70 years. Mean age was 58.28 years. Age group 61-70 years had the maximum number of patients and totaled 64. The group comprising 51-60 years had 58 patients from the study population. The least number of patients were seen in the age group 41-50 years which accounted for 28 patients.

Gender Distribution

Table 7: Gender wise distribution of patients

Gender	Number	Percentage (%)
Male	85	56.67
Female	65	43.33
Total	**150**	**100.00**

The study population showed a higher male preponderance with 56.67% male patients and 43.33% female patients.

Figure 8: Gender wise distribution of patients

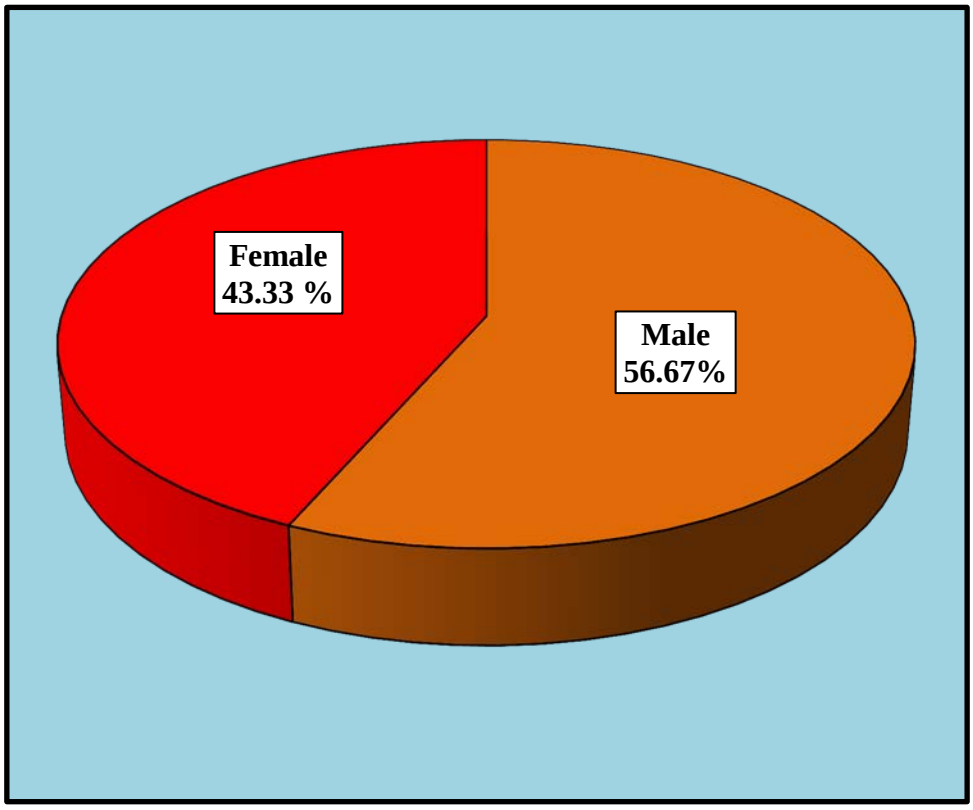


Table 8: Inhaler use wise distribution of patients

Inhaler use wise distribution	Number	Percentage (%)
Yes	118	78.67
No	32	21.33
Total	**150**	**100.00**

Inhaler therapy was prescribed to 118 patients indicating that 78**.**67% of the study population was prescribed inhaler therapy.

Figure 9: Inhaler use wise distribution of patients

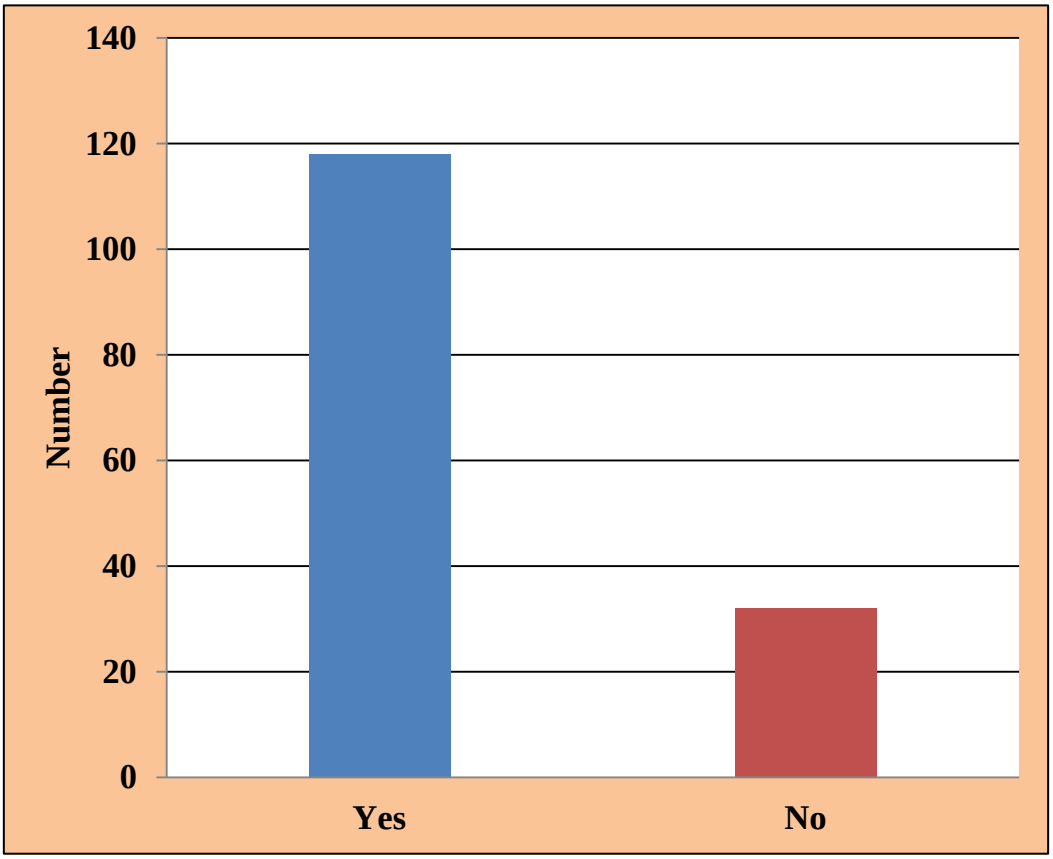


Table 9: Injection use wise distribution of patients

Injection use wise distribution	Number	Percentage (%)
Yes	115	76.67
No	35	23.33
Total	**150**	**100.00**

Injections were administered to 115 patients, which accounted for 76.67% of the study population.

Figure 10: Injection use wise distribution of patients

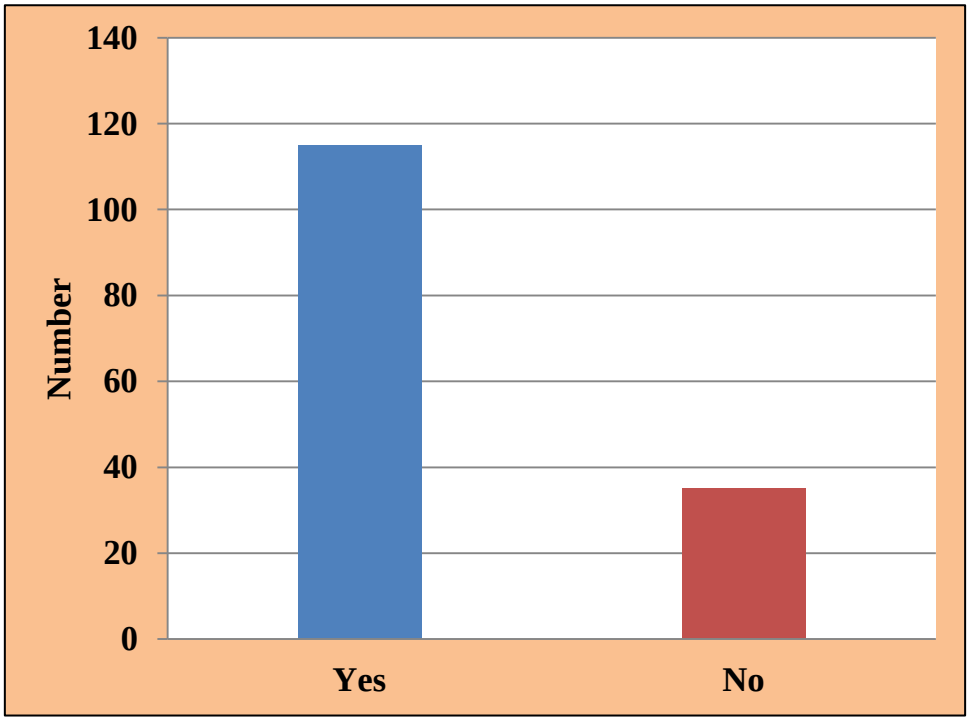
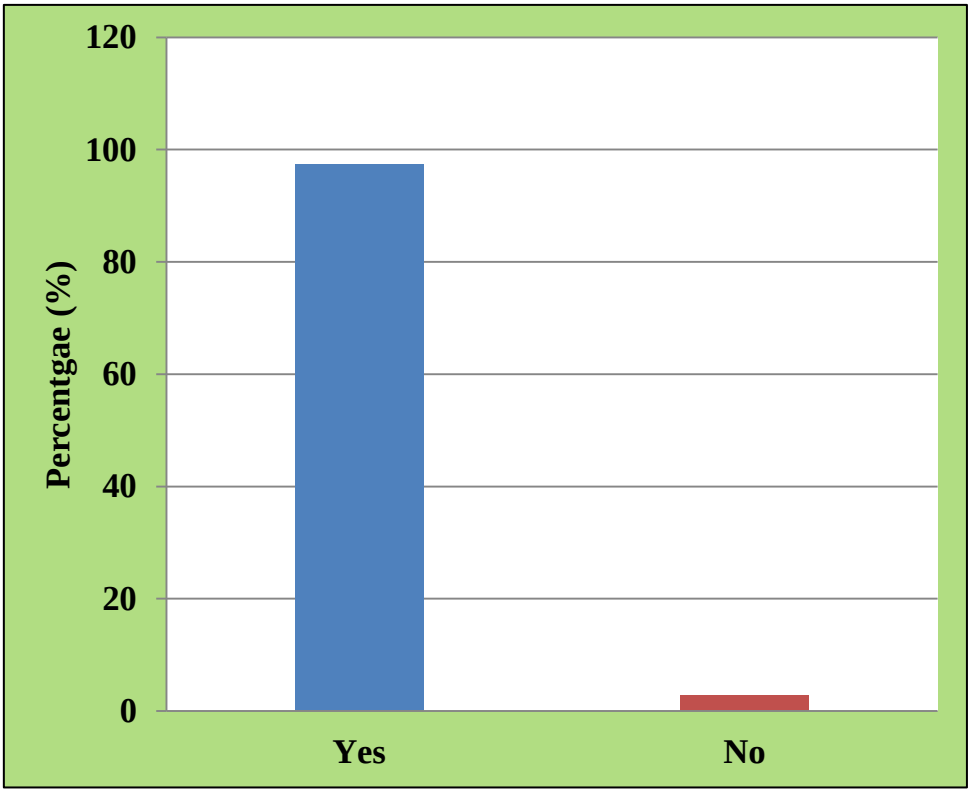


Table 10: Nebulization use wise distribution of patients

Nebulization use wise distribution	Number	Percentage (%)
Yes	146	97.33
No	4	02.67
Total	**150**	**100.00**

Nebulization was prescribed to 146 patients indicating that 97.33% of the study population received nebulization therapy and that it was widely preferred.

Figure 11: Nebulization use wise distribution of patients



Prescribing Indicators Data

a) Average number of drugs per patient

Total number of different drugs prescribed = 650 = **4.33**

Number of patients surveyed 150

b) Percentage of drugs prescribed by generic name

Number of drugs prescribed by generic name X100= 447/650= **68.76%**

Total number of drug prescribed

c) Percentage of patients with injection prescribed

Number of patients with injection prescribed X100= 115/650= **17.69**

Total number of drug prescribed

d) Percentage of patients with inhaler prescribed

Number of patients with inhaler use X100 = 118/150= **78.67**

Total number of patients

e) Percentage of patients with oral prescribed

Number of patients with oral prescribed X100 = 243/650= **37.38**

Total number of drugs prescribed

f) Percentage of patients with nebulization

$$\frac{\text{Number of patients with nebulization used}}{\text{Total number of patients}} \times 100 = 146/150 = \mathbf{97.33}$$

g) Percentage of drugs prescribed from Essential drug list (EDL)

$$\frac{\text{Number of drugs prescribed from EDL}}{\text{Total number of drugs prescribed}} \times 100 = 408/650 = \mathbf{62.76}$$

Table 11: Summary of prescribing indicators data

Prescribing indicator assessed	Average/Percentage	WHO standard
Average number of drugs per patient	4.33	2-3
Percentage of drugs prescribed by generic name	68.76%	100%
Percentage of patients with injections	17.69%	16-20%
Percentage of drugs prescribed from EDL	62.76%	80-100%

Polypharmacy was observed in the prescriptions (4.33) compared to WHO value (2-3).

Drugs were prescribed by generic name (68.76%) which is below the WHO value (100%).

Injection use was 17.69% which meets the WHO criteria (16-20%).

Prescription of drugs from EDL (62.76%) which is below the WHO criteria (80-100%).

Utilization of various classes of drugs in COPD

Table 12: Frequency of distribution of drugs in each prescription

Number of drugs in each prescription	Number	Percentage (%)
Three drugs	20	13.33
Four drugs	61	40.67
Five drugs	24	16.00
Six drugs	45	30
Total	**150**	**100.00**

Prescriptions with a combination of 4 drugs amounted to 61 prescriptions and accounted for 40.67% of the total prescriptions.

Prescriptions with a combination of 6 drugs accounted for 30% of the total prescriptions.

Prescriptions with a combination of 5 drugs accounted for 16% of the total prescriptions.

Prescriptions with a combination of 3 drugs accounted for 13.33% of the total prescriptions.

Figure 12: Frequency of distribution of drugs in each prescription

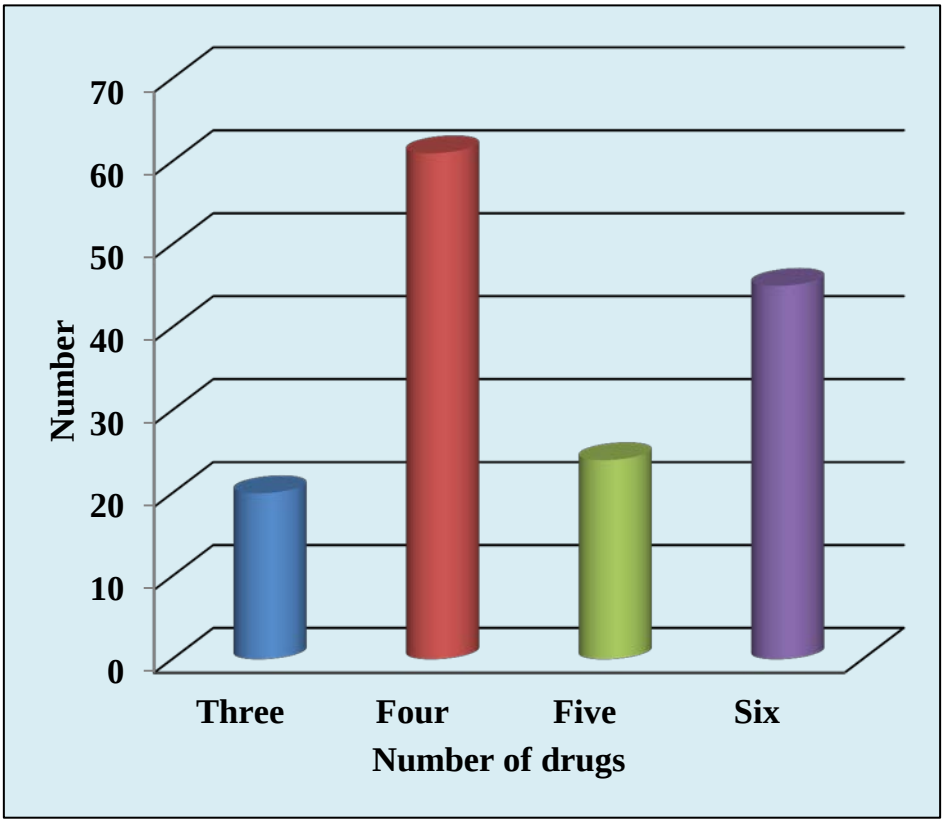


Table 13: Most commonly used drug class in the study population

Most commonly used drug	Number	Percentage (%)
Beta-2 agonist	149	40.38
Anti-cholinergic	0	00.00
Deriphyllin (Hydroxyethyl theophylline)	101	27.37
Steroid	0	00.00
Combination	119	32.25
Total	**369**	**100.00**

Beta-2 agonist was the most commonly used class of drug (n=149, 40.38%). No anti-cholinergic or steroid monotherapy were given. Combination of drugs used (n=119, 32.25%).

Figure 13: Most commonly used drug class in the study population

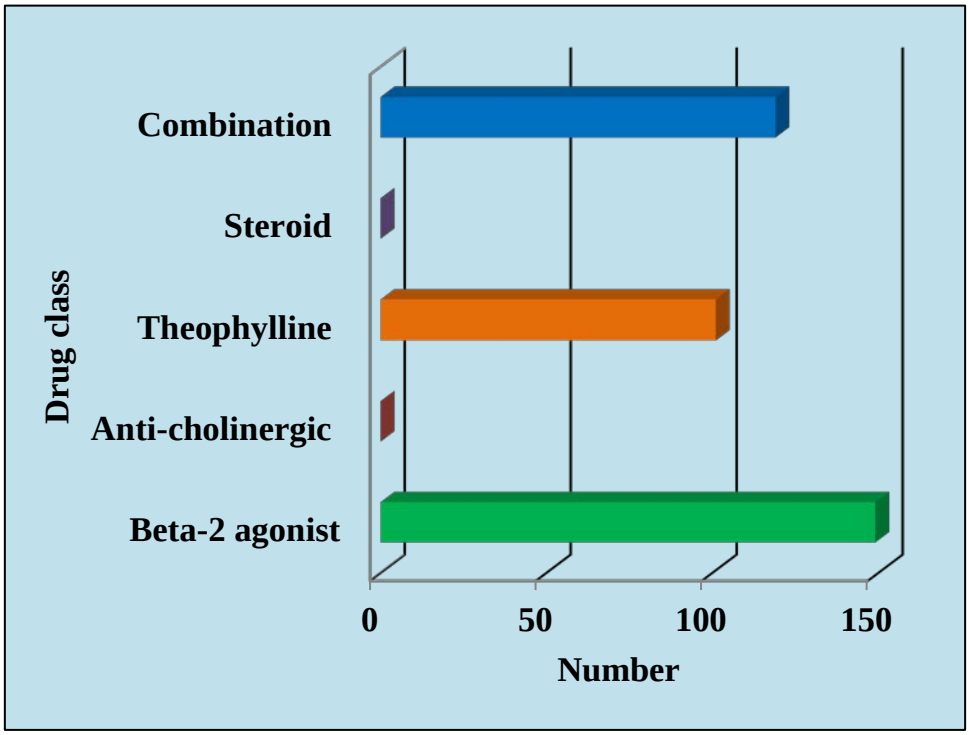


Table 14: Most commonly used drug by oral route of administration

Most commonly used drug by oral route	Number	Percentage (%)
Salbutamol	148	59.44
Deriphyllin (Hydroxyethyl theophylline)	101	40.56
Total	**249**	**100.00**

Commonest drug prescribed orally is Salbutamol n=148. Deriphyllin was prescribed to 40.56%.

Figure 14: Most commonly used drug by oral route of administration

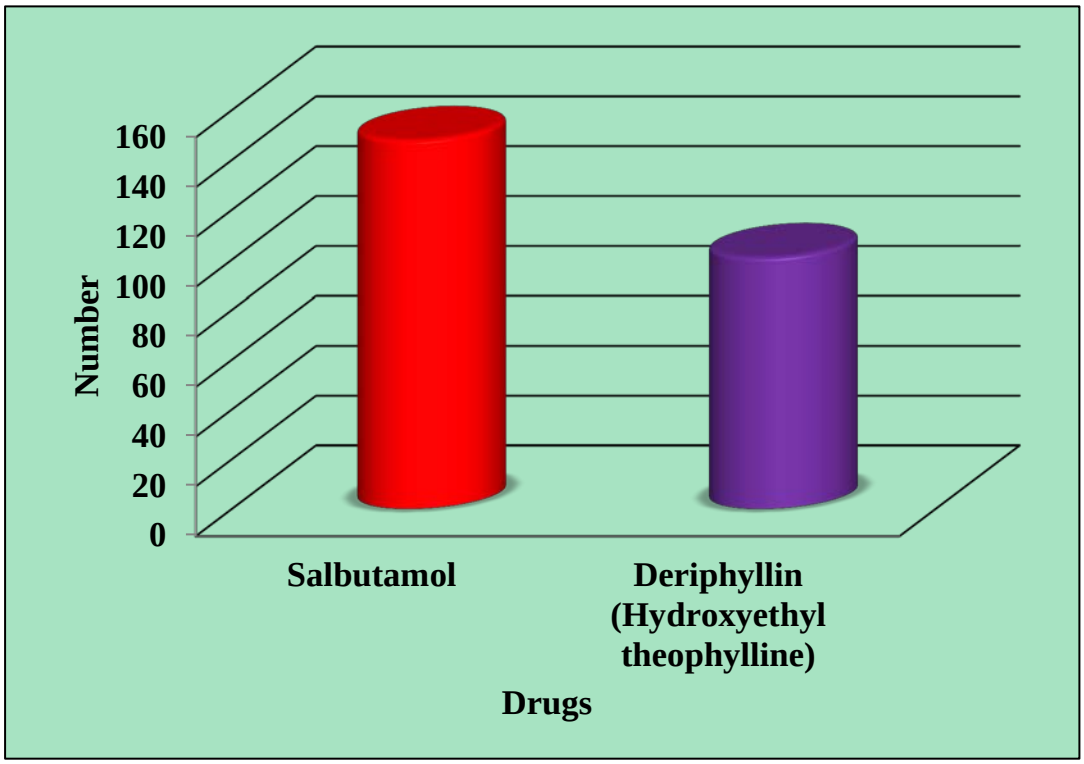


Table 15: Most commonly used drug by inhalation

Most commonly used drug by inhalation	Number	Percentage (%)
No inhalation	31	20.67
Levosalbutamol	53	35.33
Salbutamol+ipratropium	56	37.33
Formoterol+Fluticasone	10	06.67
Total	**150**	**100.00**

The combination of Salbutamol and ipratropium was the most commonly prescribed drugs (n=56, 37.33%). The least prescribed was formoterol and fluticasone combination (n=10, 6.67%).

Table 16: Most commonly used drug by injection

Most commonly used drug by injection	Number	Percentage (%)
No injection	34	22.67
Dexamethasone+Deriphyllin	116	77.33
Total	**150**	**100.00**

Dexamethasone and deriphyllin combination was prescribed as injection to 116 patients.

Table 17: Most commonly used drug by nebulization

Most commonly used drug by nebulization	Number	Percentage (%)
No nebulization	4	02.67
Salbutamol+ ipratropium	146	97.33
Total	**150**	**100.00**

Salbutamol and ipratropium nebulization was given to 146 patients.

Table 18: Frequency and percentage of patients with ADRs

Type of ADR	Number	Percentage (%)
Tremor	5	62.50
Hoarseness of voice	1	12.50
Bitter taste	1	12.50
Hypersensitivity	1	12.50
Total	**8**	**100.00**

Total ADRs reported was 8. Tremor was the most common ADR observed in 5 patients.

Figure 15: Frequency and percentage of patients with ADRs

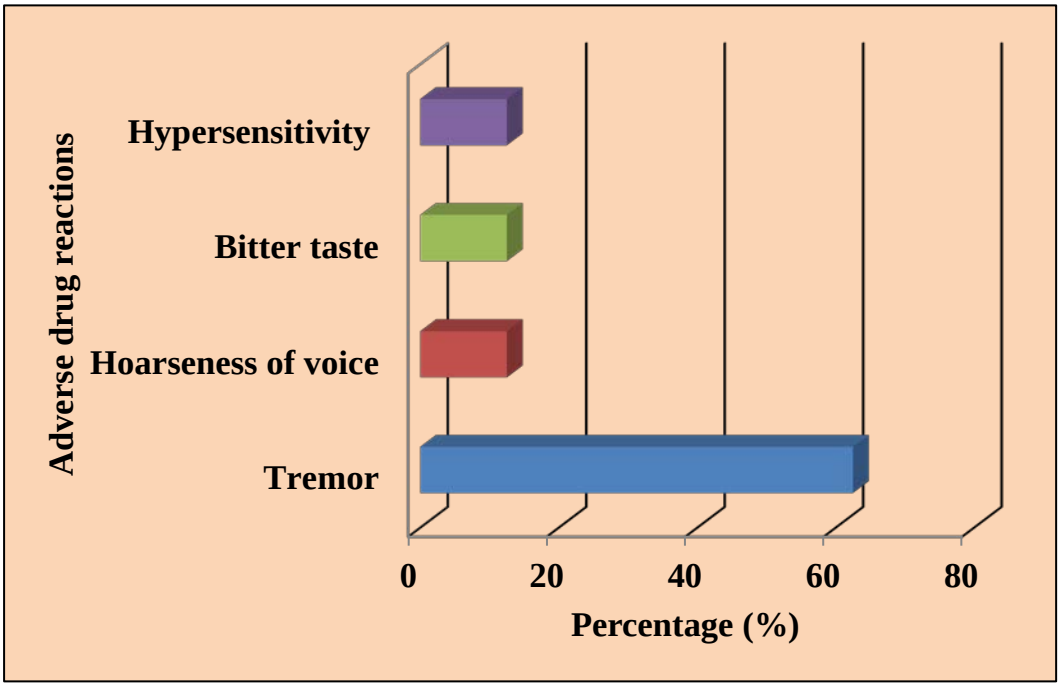
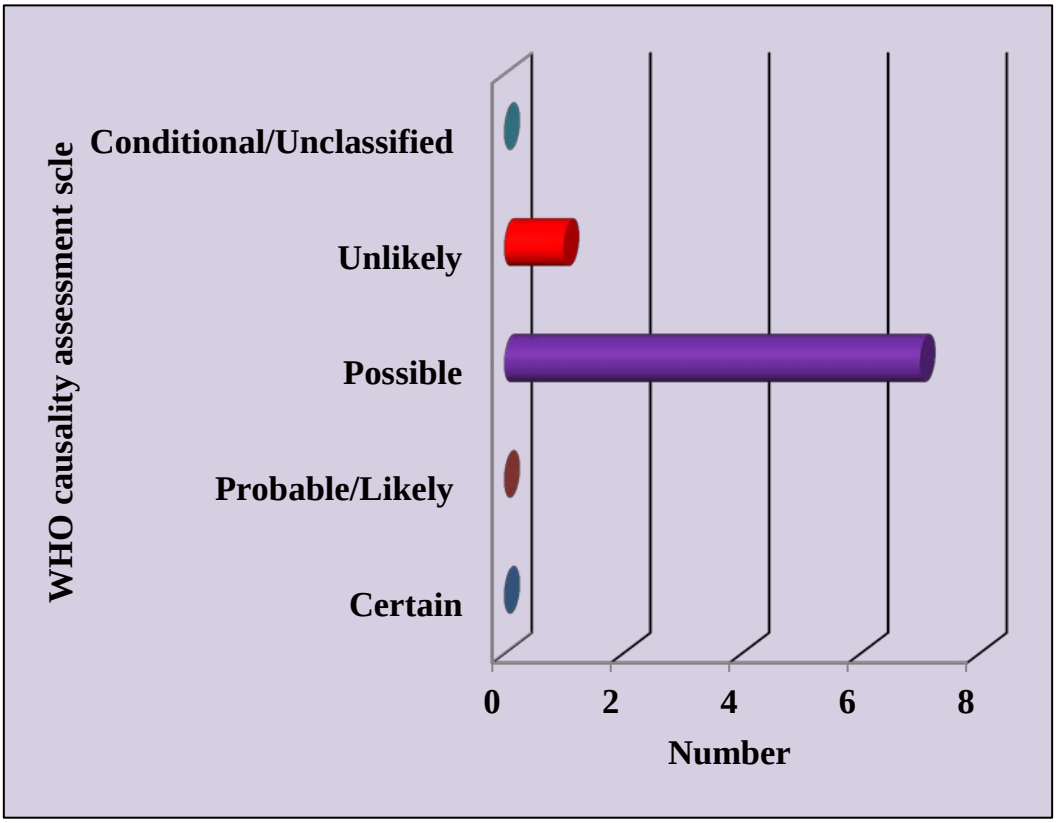


Table 19: Causality Assessment of ADRs according to WHO

WHO Causality Assessment Scale	Number	Percentage (%)
Certain		
Probable/Likely		
Possible	7	87.5%
Unlikely	1	12.5%
Conditional/Unclassified		
Total	**8**	**100.00**

The maximum ADRs observed were possible according to WHO causality assessment.

Figure 16: Causality Assessment of ADRs according to WHO



DISCUSSION

The present study was undertaken to determine the drug utilization pattern and safety profile in the management of COPD in the General Medicine Outpatient Department in Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari district. The objective of the study was to determine the utilization of drugs with the reference of WHO drug use indicators, prescribing trends and assess safety profile.

Treatment of COPD with multiple complications using minimal number of medications poses a challenge to the treating physician as treatment requires specific combination of drugs. Drug combinations can be prescribed for treatment as well as prophylaxis of COPD. In the treatment of COPD, it is essential to maintain a balance between the number of medications prescribed and achieving treatment goals with minimal adverse effects.

COPD with co-morbid conditions necessitated the use of various classes of drugs that include directly and indirectly acting bronchodilators, anti-secretary agents, antihistamines and antimicrobial agents. The administration of these groups of drugs relieves bronchoconstriction, secretion and infection. Combination of drugs in COPD management plays a pivotal role in reducing morbidity and mortality. In the present study, all the above classes of drugs were prescribed for the treatment of patients diagnosed with COPD without other complications.

COPD can affect any age group but it is most commonly seen affecting middle aged and elderly population. Morbidity and mortality in COPD can be reduced with early diagnosis and initiation of treatment. Pattern of drug utilized to treat COPD varies pan India. Drug availability, socioeconomic status of the patient, area of living and co-morbidity conditions can influence the prescription pattern of drugs in COPD. This present study was conducted to observe the drug utilization pattern and their safety in the south Indian population diagnosed with COPD.

The present study included 150 patients with COPD. Patients in the age group 40-70 years were included in the study. 42.66% was in the age group 61-70 years. Only 28 people were aged between 40 to 50 years. Parbiaz AK[55] and Lopez AD, et.al.[56] study also showed that the prevalence of COPD was more in the age group 60-70 years with 53%. The impact of gender on expression of COPD has received even lesser attention in India. Tobacco smoking is an important factor for the development of COPD in males whereas indoor air pollution and biomass fuel may play a significant role in the development of COPD in women. Jain NK, et.al.[57] studied 720 patients regarding etiological and risk factors leading to COPD with correlation to gender. The study results concluded that COPD was more common in men compared to females. Silverman EK, et al.[58] study had the same observations. Similar results were observed in the present study wherein males were afflicted more than females (56.67% males and 43.33% females) with COPD.

The choice of inhaler device for patients with COPD depends upon multiple attributes. Efficient delivery of inhaled medication is essential for the success of COPD therapy. The inhaler device may contribute to optimal drug delivery and also impact patient adherence. A wide range of inhalers are available, including pressurized metered dose inhaler (pMDI), dry powder inhaler, nebulizers, and spinhaler. Advantages and disadvantages are present for each type of device. In this study, maximum number of patients used inhaler which contributes to 78.67%. Maithu M, et.al.[59] studied use of inhalers in 245 COPD patients. The study results expressed similar percentage use of inhalers. Newman SP study showed 76% of people used inhalers in the treatment of COPD. The present study results and the above study results indicate that inhalers are the most commonly preferred route for drug delivery in COPD management.

Rational treatment depends upon the selection of proper route for the administration of drugs based on the severity of COPD. Systemic route of administration has long been a standard for the treatment of COPD; however, the optimal strategy for dosing and administration is continually debated. Andrew Woods J, et.al.[60] observed that systemic administration of drugs have significantly relieved the symptoms of COPD by improving airflow, decreasing treatment failure, reducing the risk of relapse, and curtailing the length of hospital stay. Further attacks of COPD can be prevented by therapy with oral or inhalational medication. Recent data suggested that initiation of parenteral therapy has more efficacy in the traditional treatment guidelines of COPD. In

this study population, 115 members were administered injections. Only 35 were not given injections. This study results significantly correlated with other studies Lindenauer PK, et.al.[61]

Nebulization based therapy is the cornerstone of treatment for patients with COPD. Appropriate use of nebulization has significant impact compared to other modes of administration in the COPD management. GOLD strategy document recommends nebulizers for specific patient populations (patients with very low inspiratory flow rate in whom nebulizer treatment may provide more benefits than inhalers. Further GOLD recommends evaluating the benefits of nebulizer treatment symptomatically and continuing treatment as long as similar benefits are not achievable by simpler, cheaper, and more potable alternatives. Dhand R, et.al.[62] and Berlinski A[63] studies showed beneficial effects of nebulization use in the treatment of COPD. In both studies nebulization was the preferred mode of drug administration for COPD treatment with maximum number of patients receiving nebulization. In the present study, maximum patients received nebulization (n=146).

Drug utilization studies can provide insight into a pattern, quality, determinants and outcome of drug use. In this study, a total of 150 prescriptions were observed for prescribing indicators. 4.33 was the average number of drugs per patient. Mahadeo PS, et.al.[64] studied prescription pattern of drugs in 284 COPD patients. This study data concluded that average number of drugs per prescription were 7. It is higher than the WHO norms. In a study done by Mazher M, et.al.[65] results showed 5 drugs per prescription. In this

present study, the average number of drugs prescribed was 4.33. This is slightly similar to the average of both the above mentioned studies. This indicator is very important as it indicates the degree of polypharmacy and providing insight for review and educational intervention in regular practice. WHO has guidelines in place for combination of drugs for treatment of COPD.

Generic drugs are most commonly used in the treatment of COPD because of their cost-effectiveness. According to WHO, there should be 100% usage of generic drugs in the treatment of COPD. In some conditions, it cannot be followed due to unavailability of generic drugs as mono or in combination therapy. Kothai R, et.al.[66] conducted a study on 150 COPD patients. They observed 36.66% of drugs were prescribed by generic name, which is lower compared to WHO guidelines. Tamas AGH, et.al.[67] study showed 42.56% of drugs were prescribed by generic name. In the present study, 68.76% of the drugs were prescribed by generic name. These studies have not measured up to WHO guidelines. These observations may be due to unavailability of generic drugs. In COPD most of the drugs were used in combinations. These combinations may not be available as generic drugs and due to this lesser percentage was observed in the studies. In polypharmcy prescriptions, some drugs may be prescribed other than generic drugs for better patient safety and efficacy.

The burden of disease in terms of morbidity was obtained for each country from the Institute for Health Matrix and Evaluation (IHME) database. This is the most recent and reliable source of data on burden of disease which

has been frequently cited in global studies. COPD is one of the highest ranked disease in low income countries. To identify treatment of different stages of COPD two major guidelines were considered. Treatments were assigned either to gain and maintain disease control or to manage episodes. To maintain uniformity in the treatment, WHO prepared essential drug list for COPD.

A study by Yaser TB, et.al.[68] on COPD patients showed nearly 90% of drugs were prescribed from essential drug list in the management of COPD. It was lesser in low income areas of India. The average percentage of drugs prescribed from essential drug list is 80-90% across India. In the present study, 408 drugs were prescribed from essential drug list, which contributes to 62.76% of essential drug use. Cameron A, et al.[69] study observed 75.34% of drugs were prescribed from essential drug list. There is a variation in the studies regarding prescription of drugs as per essential drug list.

According to WHO guidelines 80-100 % drugs should be prescribed from the EDL. The present study results showed less percentage of essential drugs in the prescriptions. This could be as a result of unavailability of essential drugs in the form of combination during the study period.

Currently, there are no specific classes of drugs available for COPD to reduce the progressive decline in lung function which is the hallmark of this disease. The present pharmacological treatment of COPD is symptomatic and it is mainly based on various classes of drugs mainly bronchodilators, anti-secretary agents, antihistamines, anti-inflammatory (glucocorticoids) and

antibiotics. Glucocorticoids are not generally recommended for patients with stable mild to moderate COPD due to their lack of efficacy, side effects.

A total of 650 drugs were prescribed in the present study for 150 patients. A combination of 3 to 6 drugs was used for better treatment outcome. Pauwels RA, et al.[70] suggested a combination of various classes of 3 to 4 drugs have shown better treatment outcome than combination of two drugs of different class or three drugs in the same class. Rennard SI[71] concluded in his study that a combination of different classes of drugs reduced the progression of COPD and relieved the symptoms compared to monotherapy. The current study observations showed 61 patients were prescribed 4 drugs per patient and 45 patients were prescribed 6 drugs per patient. 20 and 24 patients were prescribed 3 and 5 drugs each respectively.

COPD guidelines provide advice about the appropriate use of various medications in treating patients with this condition. Combination of drug therapy is recommended by GOLD guidelines for the better management of COPD patients. The common classes of drugs used in pharmacological management of COPD are beta-2 agonist (salbutamol, salmeterol, formoterol), anticholinergic drugs (ipratropium and tiotropium), methylxanthines (deriphyllin), inhaled glucocorticoids (fluticasone, budesonide), oral glucocorticoids (prednisolone, methylprednisolone), parenteral glucocorticoids (dexamethasone) and phosphodiesterase 4 inhibitors (roflumilast) Michel R.[72]

Bronchodilators play a major role in the treatment of COPD. Indirectly acting bronchodilators will increase the effect of directly acting bronchodilators. The bronchodilator effect can be enhanced with the co-administration of deriphyllin. Inflammation is also one of the major symptoms in COPD which can be suppressed with the use of glucocorticoids. The above classes of drug combination play a major role in the treatment of COPD. Donnell DE, et.al.[73] study evaluated use of bronchodilators in 23 patients with COPD. He concluded that bronchodilators reduce mechanical restriction, increased ventilator capacity, decreased respiratory discomfort and increased the exercise capacity. All the patients showed significant result compared to placebo. Qaseem A, et.al.[74] observed that there is an improvement in COPD symptoms of upto 60% with the usage of beta-2 agonist. In this present study, 149 patients were given beta-2 agonists.

Methylxanthines are directly acting bronchodilators. These drugs are mainly combined and administered with beta-2 agonist. In this class, deriphyllin was used with combination of salbutamol in the treatment of COPD. Mitsuko K, et.al.[75] suggested combination of short acting beta-2 agonist with deriphyllin improves the patient condition effectively. Graham D, et.al.[76] study combined low dose of xanthines with other drugs in the treatment of COPD. This study includes 1424 patients, in that maximum number of patients showed better treatment outcome compared to other combinations. The present study also was similar to the above mentioned studies where 101 patients out of total 150 patients were given deriphyllin with the combination of

beta-2 agonists. 119 patients have been given a combination of different classes of drugs.

Long acting glucocorticoid (dexamethasone) with deriphyllin was administered as an injection to 116 patients. This steroid suppresses the inflammation and deriphyllin increases the action of beta-2 agonist and dilate the bronchus. Combination of anti-inflammatory with directly acting bronchodilator plays a major role in severe and acute COPD management. Mohammad EA, et.al.[77] administered 34 COPD patients with dexamethasone. They were observed to increase the respiratory rate and decrease dyspnoea. Koc I et al[78] administered dexamethasone to COPD patients for 3 months. He observed it decreased the inflammation, cytokine formation and improvement in the symptoms of COPD. Dexamethasone was given in the form of injection in this study and similar effect was observed in comparison to the above studies.

In our study, the frequency of ADRs was 8. The most common ADR was tremors, 5. In this study, Salbutamol was the most commonly used drug. The known adverse effect of Salbutamol was tremors. In a study by Sestini P, et.al[79]., the causality assessment of ADR had been done using the WHO scale in which majority were possible (95.46%) with a less number of certain, probable reactions. Similarly in our study, more frequency was towards possible ADRs (87.5%).

Limitations of our study were less sample size, socioeconomic status of the patients were not analyzed and defined daily dose was not calculated which could have provided more information on total cost of management of COPD.

CONCLUSION

The pattern of drugs used in COPD was studied in 150 patients of Sree Mookambika Institute of Medical Sciences from the period of January 2017 to January 2018. From our study findings, we were able to conclude that:

1. Mean age of study population was 58.28 years.
2. Male preponderance was higher compared to females.
3. Average number of drugs per patient was 4.33, which was higher than WHO standards (2-3).
4. 68.76% of drugs were prescribed with generic name which was lower than WHO standard (100%).
5. Only 17.69% of drugs were prescribed by injection, which is similar to WHO standard (16-20%).
6. 62.76% of drugs were from EDL which was lower than WHO standard (80-100%).
7. 78.67% of patients used inhaler.
8. 76.67% of patients were administered injections.
9. 97.33% of patients used nebulization.
10. 61 patients had prescriptions where 4 drugs were prescribed.

11. Most commonly used class of drugs were beta-2 agonist, 149.

12. Among oral medications, salbutamol was most common, 148.

13. Among combination therapy, salbutamol + ipratropium was most common, 56.

14. 116 patients were prescribed dexamethasone + deriphyllin.

15. Salbutamol + ipratropium were the maximum prescribed by nebulization, 146.

16. Most common adverse effect was tremor, 5.

17. Maximum ADR was possible (87.5%) as per WHO causality assessment scale.

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INSTITUTIONAL HUMAN ETHICS COMMITTEE

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES,
KULASEKHARAM, TAMILNADU

Communication of Decision of the Institutional Human Ethics Committee(IHEC)

SMIMS/IHEC No:1 /Protocol no: 25 /2016

Protocol title: PATTERN OF DRUG USE AND THEIR SAFETY PROFILE IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN A TERTIARY CARE HOSPITAL
Principal Investigator: Dr. S.Ramakrishnan
Name& Address of Institution: Department of Pharmacology Sree Mookambika Institute of Medical Sciences, Kulasekharam ☑ New review ☐ Revised review ☐ Expedited review
Date of review (D/M/Y): 15.12.2016 Date of previous review , if revised application:
Decision of the IHEC: ☑ Recommended ☐ Recommended with suggestions ☐ Revision ☐ Rejected
Suggestions/ Reasons/ Remarks:
Recommended for a period of : one year

Please note*

- Inform IHEC immediately in case of any Adverse events and Serious adverse events.
- Inform IHEC in case of any change of study procedure, site and investigator
- This permission is only for period mentioned above. Annual report to be submitted to IHEC.
- Members of IHEC have right to monitor the trial with prior intimation.

Reneegaljangadhar

Signature of Member Secretary IHEC

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES ★ KULASEKHARAM ★
IHEC
Date 21/12/16

CONSENT FORM

Title of the project: "Pattern of drug use and their safety profile in the management of COPD in a tertiary care hospital."

Participant's name: Address:

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

(I also consent / do not consent to use my stored biological samples for future scientific purposes: Yes/ No – if applicable)

Signature of the participant: _____ Date: _____

Signature of the witness: _____ Date: _____

Name and address of the witness:

Signature of the investigator: _____ Date: _____

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

Kulasekharam, Kanyakumari District, Tamil Nadu, India – 629161

Department of Pharmacology

CASE RECORD FORM

Title of the Study: "Pattern of drug use and their safety profile in the management of COPD in a tertiary care hospital."

Subject number: O.P.No.: Date:

Age: Sex: M / F

Address with contact number:

Presenting complaints:

Diagnosis:

Details of medications prescribed

S.No	Drug prescribed by generic/brand name	Dose	Frequency	Route	Duration

Adverse effects (if any) :-

Signature of the Principal Investigator

ADR ASSESSMENT SCALES

Scale 1: WHO CAUSALITY ASSESSMENT OF SUSPECTED ADVERSE DRUG REACTIONS

(The Uppsala monitoring centre 2002)

Term	Description
Certain	A clinical event, including laboratory test abnormality, was occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable/ Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Conditional/ Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
Unassessible/ Unclassifiable	A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhavan, ITO, Kotla Road, New Delhi
www.cdsco.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique no.

A. Patient Information

1.Patient Initials _____

2.Age at time of Event or date of birth _____

3. Sex ☐M ☐ F

4. Weight ____Kgs

12. Relevant tests / laboratory data with dates

B .Suspected Adverse Reaction

5. Date of reaction stated (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

- ☐ Death (dd/mm/yyy)____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenitial anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes

- ☐ Fatal
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ Other (specify)____

C.Suspected medication(s)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address :_____
_____
Pin code : _____ E-mail _____
Tel. No. (with STD code): _____
Occupation _____Signature _____

17. Causality Assessment

18. Date of this report (dd/mm/yyyy)